UNITED STATES FOOD AND DRUG ADMINISTRATION

CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

PART 15 HEARING:
DRAFT GUIDANCES RELATING TO THE REGULATION OF HUMAN CELLS, TISSUES, OR CELLULAR OR TISSUE-BASED PRODUCTS

Bethesda, Maryland

Monday, September 12, 2016

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Session 1 Speakers (in order of appearance):

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Alliqua Biomedical

PAMELA VETTER
Allosource

TIMOTHY GANEY
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MARY PAT MOYER
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DR. MUKESH KUMAR
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STEVEN BRODY, M.D., Ph.D.
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FDA Presentation on September 8, 2016, Workshop, "Scientific Evidence in Development of HCT/Ps Subject to Premarket Approval":

STEVEN R. BAUER, Ph.D.
Food and Drug Administration

Session 2 Speakers (in order of appearance):

MARYANN CHIRBA
Boston College Law School

PARTICIPANTS (CONT'D):

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Case Western University

KEITH MARCH
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JULIE ALLICKSON
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National Spine and Pain Centers-VA

Session 3 Speakers (in order of appearance):

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Academy of Regenerative Practices

MICHAEL WERNER
Alliance for Regenerative Medicine

PARTICIPANTS (CONT'D):

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P R O C E E D I N G S

(9:00 a.m.)

DR. WITTEN: I would ask everybody to take their seats. We have a full agenda today, so I would like to get started. I'd like to start by saying good morning to both the attendees in the conference center and to those viewing the hearing through our live webcast. Welcome to the Part

Hearing on the Draft Guidances Related to the Regulation of Human Cells, Tissues, and Cellular and Tissue-based Products. I'm Dr. Celia Witten, deputy director of the Center for Biologics Evaluation and Research. I will serve as a presiding officer for this hearing.

Before we begin, I have a few housekeeping announcements. Please turn off any mobile devices as they may interfere with the audio in this room. We ask that all attendees sign in. Upon sign in, you will be or have been given a name tag indicating whether you're speaking or attending, but not speaking. The hearing is scheduled from 9:00 a.m. until 5:00

p.m. today and tomorrow. Restrooms are located in the lobby.

Today we are planning for one 20-minute break during the morning session and one 15-minute break during the afternoon session. Today's lunch break is scheduled from 11:57 to 1:12 p.m., and I say those times just to make the point that we are really on a tight agenda today.

There are a variety of lunch options in the cafeteria in the basement of this building. As we are on a tight schedule, we'll resume promptly. Immediately before the lunch break, Dr. Steven Bauer, chief of the Cellular and Tissue Therapy Branch in the Division of Cellular and Gene Therapies in the Office of Cell Tissue and Gene Therapies at CBER, will speak. He will provide a summary from the September 8th FDA Workshop on Scientific Evidence in Development of Human Cells, Tissues, and Cellular and Tissue-Based Products that are Subject to Pre-Market Approval.

The purpose of the hearing today is to

obtain broad stakeholder input on the following four draft guidances related to the regulation of human cells, tissues, and cellular, and tissue-based products, or HCT/Ps. They are the same surgical procedure exception guidance: questions and answers regarding the scope of the exception; minimal manipulation of human cells, tissues, and cellular and tissue-based products; human cells, tissues, and cellular and tissue-based products from adipose tissue regulatory considerations; and lastly, homologous use of human cells, tissues, and cellular and tissue-based products, draft guidance for industry and FDA staff.

I'd like to provide some brief background on the regulatory framework. In 1997, FDA first announced a proposed approach to the regulation of HCT/Ps. FDA then engaged in notice and a comment rulemaking. The resulting regulatory framework became fully effective May 25, 2005. Since that time, FDA has issued a number of guidance documents to further assist

stakeholders in implementing the regulations. We've received requests from stakeholders for further clarification, including to explain further our current thinking related to whether an HCT/P is subject to pre-market approval. Specifically, stakeholders have asked questions about the same surgical procedure exception and the meaning of homologous use and minimal manipulation.

In addition, we've received a number of questions whether the products derive specifically from adipose tissues. FDA issued these four draft guidances in response to these requests. Thus, the draft guidances are intended to provide clarity around our established regulatory framework. FDA will consider the information we obtain from the speakers participating in public hearing and from information submitted to the dockets, both before and after the hearing, as we finalize these four draft guidances.

As we described in the Federal Register notice announcing this hearing, we are interested

in comments on the scope of the four draft guidances, including the particular topics covered, the questions posed, whether there are additional issues for which guidance would be helpful, and whether FDA's recommendations for each topic are sufficiently clear and consistent within and across the documents to provide meaningful guidance to stakeholders. In addition, FDA welcomes comments that will enhance the usefulness and clarity of these documents.

I've introduced myself, but I would now like to ask the FDA panels to introduce themselves:

MR. WEINER: Hi. I'm John Barlow Weiner, the associate director for policy and also combination of products at FDA.

DR. LARD-WHITEFORD: Sheryl Lard-Whiteford. I'm the associate director for quality assurance in CBER, and also the product jurisdiction officer.

DR. ANATOL: Rachael Anatol, associate director for policy in the Office of Cell Tissue

and Gene Therapy in CBER.

MS. MALONEY: Okay, good morning. I'm Diane Maloney, associate director for policy in the Center for Biologics Evaluation and Research.

MS. ZAVAGNO: Hi, I'm Denise Zavagno. I'm with the Office of the Chief Counsel with FDA.

MS. MALARKEY: Good morning. I'm Mary Malarkey. I'm the director of the Office of Compliance and Biologics Quality at CBER.

MS. KRUEGER: I'm Angela Krueger. I'm the associate director for guidance and regulations at the Center for Devices and Radiological Health.

DR. WITTEN: Thank you. There's much interest in this area. We accepted requests to speak on a first-come, first-serve basis and every speaking slot was allocated. To those who wish to speak, but could not be accommodated, we thank you for your interest and your understanding. We encourage you to submit your full written comments to the Division of Dockets Management following the instructions in the Federal Register notice

for this meeting. We will carefully consider all comments submitted to the docket as we work to finalize the guidance documents.

We have a very full agenda which includes over 90 scheduled presentations. In order to ensure that we can complete this agenda, I will go over some ground rules.

Each registered speaker has been given a five- or eight-minute time slot on the agenda, depending on whether they represent the interests of a single stakeholder or multiple stakeholders, respectively. Given the very full agenda, we request that each speaker keep to the allocated times so we're able to keep to the schedule and allow everyone on the schedule an opportunity to speak. There's a timer to help you do this. Once you see the yellow light, you will have a minute left to wrap up your comments. If a speaker ends early, we intend to move on to the next speaker. We will need to speak to this timeframe and I thank you in advance for doing so.

We have let speakers know ahead of time

about the importance of sticking to the allotted time. Speakers can provide additional comments that go beyond their time by submission to the dockets.

This Part 15 Hearing is informal and the rules of evidence do not apply. No participant may interrupt the presentation of a registered speaker. Only FDA panel members will be allowed to ask questions of the speakers. FDA may call a speaker back for questions or clarification during the allotted times for panel questions, assuming time allows and the presenter remains available.

Public hearings under Part 15 are subject to FDA policy and procedures for electronic media coverage of FDA public administrative proceedings. Representatives of the electronic media may be permitted, subject to certain limitations to videotape, film, or otherwise record FDA's public administrative proceeding including the presentations of the speakers today. The meeting will be transcribed and the transcript will be made available at the

website specified in the Federal Register notice for this meeting. The docket will be open until September 27th, and we encourage you to submit your full written paper comments to the Division of Dockets Management, following the instructions in the Federal Register notice for this meeting.

Again, given the full agenda, we request that each speaker keep to their allotted time, so we're able to keep to the tight schedule. Thank you for your interest and participation today. We look forward to a productive public hearing.

We will now proceed with the presentations. The first speaker represents Alliqua Biomedical. Thank you.

DR. SMIELL: Good morning. I'm Dr. Janice Smiell at Alliqua Biomedical. My career as a general surgeon began by treating chronic wounds. And I did that for several years prior to moving to clinical research and industry with biologics and tissues and I've been there for over 20 years. Thank you for allowing me to speak to the panel today, to give input for consideration

on the guidance drafts.

Alliqua Biomedical is always grateful to have guidance from the agency as it considers the development of pathways for its products. And we appreciate the ability to hear from others today. We'll also provide you with written comments as part of the alliance. My comments today center around the need for further clarity and consistency among the guidelines and with the regulations, specifically on minimal manipulation and homologous use and as they relate to the use of amniotic membranes and other placental tissues.

The regulatory definition of minimal manipulation now recognizes structural versus nonstructural tissues, as well as primary function of tissue in the donor, rather than the basic functions in the recipient where there's at least one of these basic functions that's the same in both the donor and the recipient. The two concepts of minimal manipulation homologous use are interdependent and inseparable. Therefore, the definitions need to be clear and consistent

between them.

With regard to amnion, it's noted that a sheet must remain intact to provide a barrier function. A watertight barrier, however, maybe be detrimental initially allowing for fluid collection at the wound surface and there may be degrees of intactness that make more clinical sense as these products are used. Placement of a particulate made from donor amnion membrane allows for interaction of the recipient cells to completely coalesce and close any gaps that may be there. And this would provide the desired cover, an intact epithelium ultimately.

The draft guidance is silent to non-cytokine extracellular matrix proteins that are present and that do have biological functions. Functions that are actually local in their effect and different from the metabolic activities of cells -- the living cells. Minimally manipulated human extracellular matrixes do retain biologically functional components in their structure. These components have an effect on how

cells that migrate into these scaffolds will act. These cells attach and they do kick off a cascade of activity, just like they would in the donor tissue in response to an injury.

We rely on TRG recommendations to give us insight on how the agency is thinking. The TRG once recommended that cytokines in a cellular amnion product have a role in wound healing. How do we interpret then, the example that's given stating that the amniotic membrane serves as a selective barrier and retains fluid, and it is not homologous use when it's used for wound healing of dermal ulcers and defects because wound healing of dermal lesions is not a basic function of the amniotic membrane.

Which part of this recommendation makes the use of amnion and wound care, care that's provided to help those wounds heal, and non-homologous use? Is it the reference to dermal ulcers because amnion's considered to be an epidermal replacement, or is it because wound healing cannot be promoted by what's called a

structural tissue? Or is that healing requires bioactive components from living cells? Does this note a change in thinking by the FDA? We really need some help with some clearer explanations.

We assume that living cells are referenced in the regulations when we talk about those livings cells, that they're coming from the donor. Are cytokines also delivered by resident dead cells that may come with the donated tissue? Are these also a source of cytokines and are those levels of cytokines potentially systemic? A cellular human tissue from extracellular matrixes --

DR. WITTEN: Excuse me --

DR. SMIELL: -- does --

DR. WITTEN: -- I'm afraid I'm going to have to ask you to wrap this up.

DR. SMIELL: I'm sorry?

DR. WITTEN: I'm afraid I'm going to have to ask you to wrap this up.

DR. SMIELL: Okay, I'm sorry. So, in conclusion, I'd like to ask that multitasking of

human tissues be considered; that the extracellular components may have a biological function; and that we look at the conglomeration of processes and other storage agents or preservation agents be considered in their effect on the tissue. Thank you very much.

DR. WITTEN: Thank you. Our next speaker is from Allosource, representing Allosource.

MS. VETTER: Good morning. My name is Pamela Vetter and I'm the director of regulatory policy at Allosource. Allosource is one of the largest nonprofit cellular and tissue networks in the country, offering more than 200 types of cartilage, cellular, bone, skin, and soft tissue allographs to advance patient healing. On behalf of Allosource, I am pleased this morning to provide our current thinking on FDA's draft guidance related to minimal manipulation, or MM, of HCT/Ps. My comments today are a summary of two key points related to the proposed definitions of original relevant characteristics and main

function. Our thoughts are that the proposed definitions are too narrow and have the potential to impede product innovation and, more importantly, patient access to clinical treatments utilizing allograph products.

For purposes of assessing whether processing alters the original relevant characteristics of tissue relating to its utility for repair, reconstruction, or replacement, steps that the processing would amount to more than MM, the draft guidance defines what these relevant characteristics are for certain types of tissues. For example, for structural tissues, FDA has noted that examples include strength, flexibility, cushioning, covering, compressibility, and response to friction and shear.

In the draft guidance, FDA has outlined the relevant characteristics for a specific tissue type which will, in most cases, be applied across the board by the agency in addressing the question of MM. It infers that certain processes will almost always alter the original relevant

characteristics of a tissue, resulting in more than MM if performed on certain tissue types. For example, if irradiation results in crosslinking, said to alter the tensile strength of a ligament, FDA has proposed that the ligament's utility for repair has been impeded, as tensile strength is a relevant characteristic. Thus, an irradiated ligament would constitute more than MM. When, in fact, the degree of crosslinking varies with irradiation dose and studies have shown that allographs irradiated at low doses showed no significant difference in clinical success as compared to aseptically processed graphs.

Additionally, whether crosslinking impedes normal cellular remodeling is unknown. By broadly applying original relevant characteristics across the board for tissue types without considering scientific data, there could be a significant clinical impact to patients as not everyone is a candidate for autographed. There are no non- tissue alternatives for certain graphs like tendons and not all clinicians are

comfortable using aseptic or non- irradiated tissue.

The second key point is centered on the definition of "main function" as it relates to structural versus nonstructural tissues. There are several inherent issues when applying main function since tissue allographs are often used for a purpose other than their main function as determined by practitioners over the past several decades. Based on the draft guidance, FDA's position is that if you isolate cells from structural tissue, you should apply the definition of MM for structural tissue. Thus under this rationale, given that cells perform many functions, but are not generally considered to support, connect, or cushion, most uses of cells from structural tissue would be considered more than MM, while similar cells from nonstructural tissue may be considered MM.

For example, adipose was defined in the draft guidance as structural tissue. It provides padding and cushioning against shocks and stores

fat. However, adipose contains both structural and nonstructural components. By focusing solely on the main function, the draft guidance locks in the categorization of structural tissue and by doing so, inappropriately states that isolated cells from structural tissues are not to be treated like cells, but rather as structural tissue. Such a narrow descriptor of an HCT/P in relation to FDA's distinction between structural and nonstructural tissue, not only ignores scientific understanding of HCT/Ps, the individual tissues that are comprised of in their various functions, but it also has the potential to impede access to clinical treatments.

In conclusion, Allosource feels that the definitions of original relevant characteristics and main function as it relates to structural versus nonstructural tissues are too narrow. Such narrow interpretations have the potential to impede product advancement in innovation and limit the safe development of life-altering tissue products.

Thank you for the opportunity to comment today. Allosource reiterates our support for the efforts taken to collaboratively protect public health through appropriate regulation.

DR. WITTEN: Thank you. Our next speaker represents Atlanta Medical Center.

DR. GANEY: Good morning. First, I want to thank FDA for organizing this public hearing as a dialogue of interest and opinions to the use of human cells, tissue, or cellular and tissue-based products. My name is Tim Ganey, and I'm speaking today from the perspective of resident education.

As a faculty member in an urban community teaching program, my challenge is to qualify current treatments and, at the same time, support awareness of developing technologies that might result in better patient outcomes. Over the course of my tenure, I've seen steady advancement of therapeutic strategies that reflect core assets that are included in the recent draft guidance for industry. In particular, goals seeking to reconstruct, repair, and supplement tissue rather

than techniques that are focused on removing it are very encouraging.

Given the genesis of living tissue, organ development, and systems biology, it is not surprised that cell-based therapeutics have long been a hallmark strategy to heal the body. The history of cell treatments has been extensively catalogued and defined in milestones of progressive understanding. What I would ask you to note in this depiction is that there are no brackets in this timeline, either at the beginning or finalizing an end.

The ubiquity of cells in all things living has not changed, and were we to forever wait for the indivisible hole to be known before proceeding, the pace of understanding will be stunted by the derivatives of debate rather than guided by a directive to develop. Progress in understanding of cell therapy has been carried forward as marginalized risk, ensuring a greater safety in efforts to advance therapeutic benefits in patient care. Those gains are integrated into

our educational platform to support evolving practice standards that require dialogue with an ever more informed patient population. Clinical information no longer resides merely in the province of the physician. As informed patients seek physician guidance, the imperative safety remains the guarantee of doing no harm.

As an academic, and in accord with industry, I've had the opportunity to guide residents through a broad scope of in vitro and in vivo pre-clinical and clinical methods of autologous cells, autologous expanded cells, allogeneic cells, allograft, viable allograft, and various other HCT/P clinical treatments. Common to each of these regenerative medicine intentions has been the insurance of safety as the foundation and performance is the arbiter of efficacy. From the basic science perspective, aberrant pathology is best resolved in the physiology, the anatomy, psychology and pain relief shown in symptom remission, and in tissue regeneration. There are established instruments for evaluating these

performances and also for evaluating the statistical measures for comparing the proofs.

FDA conducted a workshop last Thursday, September 8th. This workshop emphasized 351 HCT/P pathways for specific indications. Both academic and industry representatives spoke to elegant examples of biologic therapies that have been successfully engineered to treat life-altering functional needs. There were also cautionary notes of poorly controlled interventions in which patients fell prey to poorly understood, if not deceptive, medical practice.

Today's caucus has been assembled to weigh the inertia in regenerative therapeutics and the balance of necessary oversight. Emerging interest in human cells, tissues, and cellular and tissue-based products has been heightened by awareness of broad applicability that has been advanced by commercial distribution and accompanied by clinical accountability. FDA has long been the gate through which novel ideas of today are likely to appear. To the timeline of

innovation, the novel ideas are likely to appear naïve by future standards, maybe the tip of an iceberg that's fashioned more from an incomplete appreciation of complex biology than weighted by underlying risk. Accepting what has been shown to be safe, the next step is to account efficacy and advance that treatment.

So the safety of autologous cells in tissue transplantation is well-established as a surgical procedure. Similarly, the use of allograft in cellular and tissue supplementation is recognized as an acceptable option in organ transplant, orthopedics, and blood transfusion among several other specialties. It is important that new clinical strategies are advanced that support safe and effective medical use. For more than 60 years, cellular- based therapeutic and biological interventions have been established as clinically relevant considerations that affect positive medical care.

The timeline moves cautiously and continuously through ideas in history. Novel

proposals are often not ordained as truth for many years. Case in point, the quantum residence that Albert Einstein recognized, spooky in his words for a century and only resolved this year as technologies evolved to appreciate it.

Today's forum may not offer the remedy for all the differences or all the understanding, but hopefully will establish a basis for accounting proofs in real-time to avoid the burden of cost and time attended to delays. With a solid foundation of safety, it is incumbent that the medical community accept this opportunity to seek and demonstrate accountable proof and rational, scientific- based, clinical evaluation. Thank you.

DR. WITTEN: Thank you. Our next speaker represents Birth Tissue Recovery.

MS. MOYER: Hello, I'm Mary Pat Moyer. I'm the CEO and chief science officer of INCELL Corporation in San Antonia, Texas. And thank you for the opportunity to make these comments today. I think all of us here have a responsibility to

the patients who are waiting for therapies and that we have to work together to find ways to do that in a more expedited fashion. And I'm sorry I couldn't be at last week's meeting, but I hear there were -- that Steve's going to present that shortly.

I think that we have opportunities here to make some specific decisions that clarify important needs for those of us who are manufacturers and are providing manufactured product of our own product, as well as manufactured product for other companies. I also think that we have an opportunity to allow for the manufacturers to work more closely with the practitioners to develop ways to better do autologous processing that meet the standards of the guidelines that have been provided.

I think that the HCT/P registration should be required for all entities who do manufacturing and that certain manufacturing practices that are currently being done on the guise of medical practice should be stopped and

that everybody needs to be registered, and that there should be a modification of Form 3356, so that that form actually has a new column that says, "Delivers those medications," so that those HTC/Ps who also deliver them to patients are indicated on the same list.

I also believe -- so these are general comments that relate to all four of the guidances. I also think that the medical doctors who are selling products that they are charging for in addition to their services have a conflict of interest. And that conflict of interest should be addressed in the context of planning for the future, for whether or not something is or isn't minimally manipulated as only one piece of it. It's, like, who owns this and what patient -- what information is being provided to the patients who are receiving this with regard to those potential conflicts of interest?

I think that there should be of an immediate action that relates to autologous HCT/Ps so that the opportunities are available for

manufacturers to provide services to clinical doctors who want to have tissues of tumors or cells from the patients or other things processed, but they don't have the tools, they don't have the capabilities, they have no idea about product release or testing or safety. Yet many of these folks feel compelled to do the work because they care about their patients. So we need to find a line where these things come together.

We shouldn't interfere with surgical practices that are appropriate for the patient, for moving this from here to there. However, if they're manufacturing, they should be registered as an HCT/P establishment.

I believe that we also need to work together to devise a registry where these various clinics that purportedly are making headway on applications are reporting what they're actually doing. And they're also reporting the outcomes, both positive and negative outcomes, not just in the context of specific clinical trials, which, of course, there should be, as well as INDs, but in

longer term follow- up with some of the patients to whom they've given these various types of treatments. And then there should be a portal that allows the patients themselves to bring information to the outcomes measures of the specific activities that are going on with regard to the therapy to the patients because patients oftentimes are told they're in a clinical trial, but they really aren't and they should be allowed to get to a portal to understand what is really happening.

I think that the work that goes toward homologous use and homologous use applications and that particular guidance is somewhat unclear in certain types of tissues and that there is some need for clarity. For example, I'll use amniotic fluid as an example. Amniotic fluid in early gestation is not the same as amniotic fluid in late gestation terminal birth. And so it has different properties and different issues with regard to handling, manufacturing, and use.

There are other regulatory

considerations for the draft guidance as it relates to adipose tissue. And I believe that only qualified, approved places that have the ability to do the manufacturing safely with product release criteria should be allowed to provide such products to patients.

I have other statements that will be in my written remarks. Thank you.

DR. WITTEN: Thank you. Our next speaker represents Intellicell Biosciences.

DR. KUMAR: Thank you. I would like to thank you for your hard work in trying to regulate HCT/Ps. Intellicell Biosciences is a small business --

DR. WITTEN: Wait, excuse me. Can you just state your name?

DR. KUMAR: My name is Mukesh Kumar, and I'm representing Intellicell.

DR. WITTEN: Thank you.

DR. KUMAR: Intellicell is a small business located in New York City that offers services for physicians using a patented method to

isolate stromal vascular fraction from a patient's lipo aspirate for re-implanting back in the same patient. Our process involves gentle sonication to disassociate the stromal vascular fractions from the blood vessels found in lipo aspirate. Our process does not use any enzymes which are widely used in other preparations of SVFs. Our process does not involve feeding cells with anything other than water or costeroids. Analysis of cell markers shows that our process does not alter the phenotype or genotype of the cells normally present in SVFs. Since the cells are used within an hour to three hours of the liposuction surgery, there is no need for using preservatives or storage agents.

We believe that we meet all the requirements of 21 CFR 1271 to be designated as an HCT/P. We also contend that our process meets the exemption described in 1271.15(b) as we are an establishment that has removed HCT/Ps from an individual and implants such HCT/Ps into the same individual during the same surgical procedure. We

follow good tissue practices, good manufacturing practices. There are no knowns observed -- known or observed clinical safety concerns due to the whole process. Our process has been used more than 550 times in the last four years without a single reported complication or adverse event associated with the use of SVFs prepared in this way.

We are here to present our perspective on FDA regulation, the guidance documents that exist for HCT/P where the donor and the recipient is the same individual. We harvest cells from one individual and implant them back in the same individual. The guidance documents are not clear about the regulatory concerns for this scenario.

We also believe that FDA has incorrectly named SVF as only a adipose-derived stem cells. Liposuction surgery involves inserting a cannula in an area surrounding the blood vessels and the process disassociates this tissue, and it's called lipo aspirate. It's different from visceral adipose tissue which is the adipose tissue that

surrounds major organs and provides support for the organs. The location of liposuction in our case is subcutaneous. Lipo aspirate in our case does not contain visceral adipose tissue. It is well recognized that subcutaneous adipose tissue acts primarily as a metabolic sync and is not considered structural tissue.

We also believe that since the process only involves saline, taking lipo aspirate in saline and concentrating it, it's minimal manipulation because it's essentially cell separation. Agency has explicitly described in multiple locations that cell separation is minimal manipulation. Agency also agrees in its guidance documents that cutting and grinding is minimal manipulation, which is how lipo aspirate is generated. Agency also agrees that tissue transplanted into the same patient during the same surgical procedure presents a low risk of contamination, and that no regulatory requirement be imposed on such processes. As I described above, most of the things we do meet those

requirements.

It is well-established in scientific literature that within each person there exist a host of cells that help and repair, and lipo aspirate or SVFs are pretty much an extraction of those cells. After the cells are implanted back in the patient, they maintain the same regenerative activities. We also, based on medical literature and of our experience, believe that the SVF offers a safe and effective option to patients for repair, reconstruction replacement, and supplementing a patient's -- to supplement a patient's injured tissue and cells.

In summary, we believe more clarity is needed for situations where the donor and recipient are the same individuals and situations like ours where cells do not appear to be altered after extraction -- after separation. We do believe FDA should further enforce good tissue practices and GMP requirements for manufacturers like us. Thank you.

DR. WITTEN: Thank you. Our next

speaker represents Johnson & Johnson.

DR. SEGAL: Good morning. I am Jay Segal, chief biotechnology officer and head scientific strategy and policy for Johnson & Johnson. On behalf of Johnson & Johnson, I thank the FDA for holding this public hearing. The FDA's risk-based approach to the regulation of human cell and tissue products, HCT/Ps, has enabled innovation while protecting the public. Nonetheless, technologies advance and lessons are learned, so it is important to update policies.

I will address two issues. First, we at J&J believe that the same surgical procedure exception should be applied more broadly. Subjecting surgical facilities to FDA registration, product applications, inspections, and other controls could be very resource intensive and intrusive. We believe that in many cases, effective and more efficient controls of same surgical procedure, HCT/Ps can be achieved through other means. Under the proposed standard for the same surgical procedure exception, as FDA

explicitly notes, many types of processing that constitute minimum manipulation would nonetheless render an HTC/P ineligible for the exception. Autologous HCT/P undergoing such minimum manipulation and homologous use within the same surgical procedure would thus be regulated as so-called 361 products, solely under 21 CFR 1271, with the intent to prevent the introduction, transmission, and spread of communicable diseases.

Thus, in these cases, FDA is proposing to regulate surgical facilities solely to prevent the spread of communicable disease. Surgical facilities already have both accreditation processes and infection control processes that are designed to prevent the spread of communicable disease. Additional regulation by FDA for the same purpose seems redundant. For those same surgical procedure HCT/Ps, which are more than minimally manipulated, the manipulation generally involves a use of one or more devices, drugs, or biologics. Clarification by FDA of the regulatory requirements for those products used to manipulate

autologous HCT/P during a surgical procedure could lead, in many cases, to more effective and efficient regulation than would subjecting the HCT/P itself to pre-market approval.

Commercial manufacturers or products used to manipulate HCT/P will often be better suited to ensure appropriate clinical testing, user training, quality, and consistency of the HCT/P than our surgical facilities. Therefore, we believe that substantially broader application of the same surgical procedure is warranted.

Second, we propose an approach to improving predictability of FDA regulatory classification decisions and timeliness of regulatory guidance for HCT/P. Predictability, consistency, and transparency are among the most important attributes of a successful HCT/P regulatory paradigm. They improve the environment for investment and help ensure appropriate and efficient product development. For these reasons, the current guidance updating process is to be applauded and we propose the following TRG process

improvements.

First, we propose formalizing a TRG process for sponsor agency interactions that would include defined timelines and enhanced communications. Second, we propose expanding content of decisions posted to the DRG website to describe the basis of the decision and help sponsors understand how related products might be regulated. Third, we propose that periodically, the TRG decisions including expanded explanatory content be circulated for public comment as draft appendices for existing guidance. These proposals would increase the ability of regulated parties to input into, to understand and to predict regulatory approaches, their products in a timely matter. The benefits to product development and to patients could be significant. Thank you.

DR. WITTEN: Thank you. Our next speaker represents Kerastem Technologies.

DR. DANIELS: Good morning. My name is Dr. Eric Daniels, and I am the chief medical officer of Kerastem Technologies located in San

Diego, California. Kerastem is the sponsor of the style trial, an active U.S. phase 2 randomized and controlled investigation of the role of adipose and its derivative stromal vascular fraction in the treatment of genetic alopecia in both woman and men. On behalf of my colleagues, peers, and the patients we were determined to impact, I'd like to thank the agency and the organizers for the opportunity to be included on today's agenda.

My comments are organized into two general categories. Number one, responsible development of HCT/Ps; and secondly, fat transplantation, the good and the bad.

Responsible HCT/P development. Attending a cell therapy conference in the early 2000s meant with 100 percent certainty discussing the following clinical development issues. What is the type of cell needed for intended biological effect? What is the dose of cells? What is the route of administration? Here we are one decade and a half later and we still lack certainty around critical issues of identity, purity and

dose response to name a few.

This historical perspective is not an indictment of the field, or meant to serve as an emergency break, but an assertion that as sponsors and investigators, we have a duty to follow the rules of the road as they relate to responsible clinical development. Ad hoc manufacturing in an operating room, using unregulated systems and tools and/or processes, as well as negligent promotion will not help uncover and, more importantly, broadly disseminate the therapeutic potential -- in this case of adipose-derived therapies. This will only come from a series of focused, well-designed, and controlled clinical trials.

As a sponsor, we are doing our part to maintain this standard. Our intent is not to obstruct the practice of medicine, but to support it on a foundation of sound science and evidence. We ask that others who seek to offer and promote products and/or therapies in this space simply be held accountable to the same level of

responsibility and standards.

Fat transplantation -- the good -- this resurgence in technique has without reservation, positively impacted a significant number of patients. Our sister organization manufacturers a market leading adipose processing system with the objective intent of body contouring, including both reconstructive and aesthetic breast surgery. This device received 510K clearance in 2010 and continues to aid physicians to shape positive clinical outcomes in both breast, as well as aesthetic reconstructive surgery. The bad, we assert that a number of manufacturers, in an effort to bypass responsible product development and take advantage of the promise of stem and regenerative therapies for commercial gain, continue to blur these reasonable rules of the road.

One very concerning trend is the expanding availability of systems where the objective intent of the manufacturer is to use repeated mechanical forces to emulsify harvested

lipo aspirate. Under the guise of resizing tissue by eliminating large adipocytes, mechanical disruption is designed and known to destroy the normal cluster of adipocytes, reticular fiber network, and small blood vessels. In short, the tissue architecture is clearly altered and, again, issues of purity, potency, and safety come into question. We assert this treatment of tissue is, therefore, beyond minimal manipulation and would not qualify for same procedure exception.

In sum, our position is clear. We support the agency's regulatory considerations for HCT/Ps from adipose tissue and ask that our peers also follow the rules of the road. Thank you.

DR. WITTEN: Thank you. Our next speaker is from LifeLink Tissue Bank.

DR. STRONG: My name is Mark Strong. I'm the associate executive director for LifeLink Tissue Bank in Tampa, Florida. And I'm also joined by Lisa Graney of Regulatory Affairs for LifeNet Health and we both are going to make comments regarding the same surgical procedure

exception, specifically the scope of the exception addressed in the guidance document. Thank you for the opportunity to make these comments here today.

Specifically to question number four. Establishments that perform a craniotomy with subsequent implementation of the bone flap to reverse a cranial defect may qualify for the exception based on the fact that they remove and store the bone and the tissue at the same facility. Establishments that ship the HCT/P, or the bone flap, to another establishment for storage and/or additional processing steps can no longer qualify for that exception. The question we would like to discuss today is if they ship that piece of tissue to an FDA registered tissue establishment, could we alter that exception?

The specific exception in 1271.51(d) states you are not required to comply with the requirements of this part if you are an establishment that does not recover screen test process label package, as displayed here on the slide. The question is what if you label the

package only with a tissue establishment's instructions and packaging materials? Every year, at least 30,000 Americans have a cranial flap removed due to trauma, stroke, cancer, emergent surgical procedures, or planned surgical procedures. FDA- registered, AATB-accredited tissue establishments offer services to clean and store these flaps and allow established standards for safe handling of tissue according to GTPs. These services better help prevent the risk of cross-contamination, reduce the risks of contamination of the flap during the storage and implantation which is often poorly regulated at those facilities.

DR. GRANEY: So at this point, what does a tissue bank or an FDA-registered facility provide for cranial flap storage? They provide a sterile pack that contains all the necessary materials for the flap to be stored or to be packaged in the OR. The paperwork that shows the detailed instructions on how to pack the cranial flap and the shipping label and information on how

to ship, as well as a shipper that contains the insulated cooler for shipment to, in this case, LifeNet Health, but to a tissue bank.

So here's an example of the types of instructions that the hospital receives. So there's really nothing left up to the hospital to determine with respect to good tissue practices. This is, firstly, they receive the shipper. It shows how to unpack it. Then it tells you how to prepare the cranial flap by basically removing hardware and rinsing. Then it goes into how to pack it in the plastic bag and then in the sterile container. And then, once it's out of the OR, how to pack it into the insulated cooler, and then package it into the shipper with the correct label information. You can also note that we have a 1-800 number that's available to the hospital staff 24/7 should they have any questions.

Importantly, I bring up two case studies. One was a 20-year-old patient who had a craniectomy at Hospital A. The flap was stored at that hospital at -80 degrees C, which is the

proper temperature. However, after recovery, the patient was transferred to Hospital B for cranioplasty, but the bone flap, when it was transported to Hospital B and then thawed from storage, it was deemed unsafe for re-implantation, and you can see that the picture on the left is the state in which the thawed cranial flap was deemed unsafe. In other words, it is completely contaminated.

The Hospital B decided to send it to the LifeNet Health for cleaning and disinfecting, so we did a pre- processing swab which showed that it has staphylococcus epidermis. And then we cleaned and disinfected it, swabbed it again, it was negative, and then there was a low dose of gamma radiation applied, and it was then stored for re-implantation. Seven months later, nothing wrong with the patient.

In the second case, it was an immune-compromised patient, so the surgeon proactively decided to have the bone flap, once removed, cleaned and stored at LifeNet Health.

Even so, the processing swabs showed staph and strep. After cleaning and disinfection, there was no infection left. Again, dosed and then re-implanted. Six weeks later and there was no issues.

So since we follow good tissue practices as a tissue bank, we would ask that the exception also apply to an establishment that ships the autologous HCT/P to an FDA- registered tissue establishment in accordance with the tissue establishment instructions. Thank you.

DR. WITTEN: Thank you. The next speaker is -- that was the speaker for LifeLink and LifeNet combined, is that the case? So our next speaker represents MedCentrus. Is that correct?

DR. MOORE: From LifeNet Health, I'm sorry.

DR. WITTEN: Oh, there's a separate LifeNet Health presentation? Okay.

DR. MOORE: Yes, they were lumped in together. So I'll be speaking today supporting

the concept and current definitions of minimal manipulation of HCT/Ps. And my name is Mark Moore. I'm senior director of scientific affairs at LifeNet Health and past chair of the Scientific and Technical Affairs Committee at AATB.

So as we'll be hearing about many times over the next few days, there are many different clinical applications of allografts, only some of which are shown here. And while allografts are widely used, they may not be clinically usable exactly as recovered from a suitably screened donor. Thus tissues may be processed often via methods requiring no more than minimal manipulation in ways to make them usable.

So these minimally manipulation processing methods are thus employed to increase the clinical utility of the allografts through, for example, reduction of risk and disease transmission, reduction of immunogenic response, shaping grafts into usable forms, reducing barriers to optimal physiological activity, and storing tissue for longer useful life and ease of

handling. In the slide at the top, you see a flowchart related to homologous use and minimal manipulation, which is an AATB draft guidance document and the title of that you can see at the top.

However, what I want to do here is focus on the definition at the bottom, which we've already seen here in the presentations with 1271.3 including two definitions of minimal manipulation of: one, for structural tissue, the minimal manipulation indicates it does not alter the original relevant characteristics of the tissue related to the tissue's utility for the intended use in the recipient with regards to the reconstruction, repair, or replacement. And that for cells in nonstructural tissue, this also means that the processing does not alter the relevant biological characteristics, again, for the intended use in the recipient.

So how do manufacturers achieve this? So typical minimal manipulation methods currently include antimicrobial disinfection, for example,

with antibiotics; detergents could be physical or chemical means; terminal sterilization, often with some form of radiation; physical alterations, including dissection, trimming, machining, and grinding; and all minimal manipulation methods. Could be de- mineralization to expose growth factors; could be de- cellularization to reduce immunogenic potential of materials; and storage preservation methods, including freezing, freeze-drying, dehydration, water replacement agents -- all recognized as minimal manipulation methods.

So, all these methods are designed, again, to improve the clinical safety and utility of the allografts while retaining their original relevant characteristics of that material as intended for use in the recipient. So, some of those retained original relevant characteristics would include biomechanical properties, such as tensile strength, compressive strengths, and isotropic strength as seen here.

Also, I would maintain that those

structural properties needed for intended repair and regeneration could be microstructural, not necessarily those macrostructural tensile strength, but microstructural properties such as providing an osteoconductive matrix or an appropriate scaffold for wound healing and physiological properties that could be retained, even in spite of a minimal manipulation; could be retention, or increased availability of growth factors, for example, with DBMs; or matrix signaling to provide a good wound healing environment, for example, with a de-cellularized matrix.

So in summary, the minimal manipulation methods described here, including physical, biochemical, and chemical treatments are designed to enhance the clinical safety and utility of allografts, while also ensuring that the allografts maintain their original relevant characteristics to support the basic function of those allografts. Thank you very much.

DR. WITTEN: Thank you. The next

speaker represents MiMedx Group.

MR. PETIT: Good morning. I'm Pete Petit and I'm chairman and CEO of MiMedx. I would like to begin by thanking Dr. Califf, Dr. Witten, and FDA staff for conducting the scientific meeting last week, and broadening the Part 15 Hearing to the two days with a larger venue that we have here today.

By way of background, I'm a medical entrepreneur who started my first company 45 years ago. That company grew to become several different publicly traded companies in health care technology and health care services. I've worked with the FDA under numerous commissioners and administrations and I've seen significant changes in the agency's interactions with industry and through these administrative changes. Therefore, I believe I'm in a good position to provide an industry perspective.

I believe that most, and I'll emphasize most, health care business executives take a logical approach to decisions related to product

innovation. That being the case, they want rules and regulations that are clearly delineated, easily interpreted, and uniformly enforced. I understand that FDA might prefer rules and regulations that are somewhat nebulous, so that they have more latitude and interpret the rules as industry innovation perhaps pushes beyond their original regulatory concepts. However, the agency needs to recognize a disruption that causes within industry. And industry recognizes a need for regulatory changes from time to time, there's a well-documented legal process for implementing changes to regulations.

I've had an opportunity to meet -- then Commissioner-elect Califf in Atlanta last December when he and Dr. Witten spoke at the International Stem Cell Conference. Commissioner Califf's message was quite clear and refreshing. My summary of his numerous comments is simply that if industry brings us science-based proposals, we will make judgments associated with those that are also science-based. From MiMedx and industry

standpoint, I want to believe that under Dr. Califf's leadership, there will be a refocus on scientific approaches to decision-making at the FDA. While I don't want to take away from the positive outlook that I currently have, I still have significant concerns about the draft guidance documents that are the subject of this Part 15 meeting.

By the way of background, MiMedx is the leading processor for amniotic tissue and since 2006 has shipped over 700,000 allografts. The clinical efficacy and cost- effectiveness of our products are supported by 32 publications, including clinical and scientific studies, randomized controlled trials, and MiMedx products have an impeccable safety record.

More than a year before publishing the draft minimal manipulation guidance documents for comment, FDA issued a main function test -- used the main function test, which is one of the new principles introduced in the new draft guidance as a basis for issuing an untitled letter from MiMedx

asserting that our micronized or powdered products were not minimally manipulated and, therefore, did not qualify for regulation under the Section 361. Prior to that untitled letter, MiMedx had undergone three FDA inspections, including a directed inspection that reviewed this status of our micronized products with input from CBER with no adverse findings.

FDA did not discuss the issuance of the untitled letter with MiMedx prior to its issuance and offered no explanation for its position. The letter itself, it took another two and a half months to obtain an explanation from the agency. At this time, there are at least 10 -- at this point in time, there were at least 10 micronized human skin dermis and bone products that were in the market.

The receipt of the untitled letter in August 2013 started a three-year process of trying to reconcile the FDA's position in the untitled letter with the regulations and the FDA's previously published interpretations. The draft

guidance on minimal manipulation and homologous use also reported major changes in tissue regulation that the federal law states can only be implemented through the formal process of notice and comment rulemaking where Congress and OMB are involved.

Therefore, we recommended FDA formally withdraw the guidance documents on minimal manipulation and homologous use, and initiate the Federal rulemaking process to give industry a reasonable time to comply with any new rules and exercise enforcement discretion on continued products for companies that enter into a diligent pursuit of the BLA process. And finally, substantially any new rule changes.

Let me stop there, Chairman, and just recommend that this fly that's --

PANEL: I know.

MR. PETIT: -- around the podium be eliminated before the next speaker comes.

(Laughter)

DR. WITTEN: Thank you.

MR. PETIT: Somewhat distracting.

(Laughter)

DR. WITTEN: Our next speaker -- thank you. Our next speaker represents the Musculoskeletal Transplant Foundation.

DR. KIM: Thank you. Actually, wait for my slides to come up.

DR. WITTEN: Perfect.

DR. KIM: Great. Thank you. My name is Dr. John Kim. I'm a breast reconstruction specialist speaking on behalf of the Musculoskeletal Transplant Foundation. I'd like to thank the FDA for allowing me to present the clinician's perspective on homologous use of acellular dermal matrix in breast reconstruction. These are my relevant disclosures.

The surgical treatment of breast cancer often requires the removal of the breast or a mastectomy. While this can be a lifesaving procedure, survivorship can be difficult because of this qualitative disfigurement that results, as you can see here. So, modern breast cancer

treatment mandates breast reconstruction. There are almost a quarter of a million new cases of breast cancer diagnosed every year. Of these, 30 to 40 percent will require mastectomy and there's been an increasing use of implant reconstruction, partly driven by the heightened awareness of the genetic basis of breast cancer.

So the particular advantage of acellular dermal matrix in this setting is that for nipple sparing mastectomies, as well as for BCRA-positive patients, direct to implant cases, and anatomic cases in which the pectoralis muscle has been attenuated, this harbors particular hope for a natural reconstruction. A traditional subpectoral implant base reconstruction requires us to place the implant underneath the pectoralis muscle seen here. However, the problem from a reconstructive point of view is you've got some tightness in the lower pull, and then oftentimes the inner portion of the breast is offset from the outer portion of the skin. So you end up with a very unnatural, high- riding breast.

The value proposition and the benefit of cutting the pectoralis muscle and using ADM in this fashion is that we can then use the acellular dermal matrix as a homologous extension of the tissue so that it can support and reinforce the lower portion of the breast, and allow the patient to get a much more natural reconstruction.

So here's a video showing the mastectomy flap, and I'm going to turn it on the underside, and what you can see there in the pink and white is the actual acellular dermal matrix. And it's been reconstituted so it looks like normal tissue because, in fact, it has become like normal tissue.

If we look at it histologically on the right side, we can see native soft tissue, and bordered on the left side is the acellular dermal matrix and on close ultrastructure, you can see that it looks and acts just like normal dermis. So our results in terms of achieving a natural reconstruction after a very disfiguring mastectomy have been enhanced by our ability to use acellular

dermal matrix and our patients are getting results that we could never get before from a mastectomy.

So the context for this is that there are over 100,000 breast reconstructions done in the U.S. every year. Of those, 80 percent require prosthesis and of those, another 80 percent are using acellular dermal matrix currently. There have been over 300 peer-reviewed publications validating breast and acellular dermal matrix reconstruction since 2005.

So in summary, per the FDA definition of dermis as a elastic connective tissue layer of the skin that provides a supportive layer of the integument, I think using this definition of the dermis, the use of ADM for breast reconstruction surgery would be considered homologous use because the purpose of acellular dermal matrix in this circumstance is to provide a supportive layer to the skin envelope. Thank you.

DR. WITTEN: Our next speaker represents Organogenesis.

DR. BILBO: My name is Patrick Bilbo. I

am senior vice president of Organogenesis where I oversee the company's regulatory affairs and government relations. Founded in 1985, Organogenesis has been a pioneer in the development of cell-based products for chronic wound healing. The company's commercialized three Section 351 allogenic, cell-based products -- Apilgraf, Dermograft, and GINTUIT -- that have been approved through the Class 3 medical device and biologics pre-market approval pathways, and have been used to treat hundreds of thousands of patients.

Organogenesis commends FDA for issuing these important draft guidances and in particular for the clarifications concerning allografts that are intended to interact with the body at a cellular level to promote wound healing. We have been concerned for some time that the market is being flooded with allograft-derived products making a wide range of unproven claims about their therapeutic efficacy and promoted for applications beyond what we believe to be for homologous use.

The importance of this issue cannot be overstated. Leg and foot ulcers that fail to heal are an immense public health challenge, typically affecting the elderly and people with diabetes. And if not effectively treated, these ulcers can lead to osteomyelitis, amputation, and death.

The availability of safe and effective treatments is, therefore, a critical public health concern. We believe that patients must receive therapeutic treatments that have met FDA's rigorous preapproval evidentiary standards. Many healthcare providers, however, are unaware of these regulatory differences in standards. Without guidance that provides clarity for industry, confusion over which products have met the strict standards will persist.

The difference between the regulatory schemes applicable to biological products on the one hand and Section 361 allografts on the other, it's stark. The regulatory requirements for biological products intended to treat chronic wounds are establishing clear guidance that

includes rigorous recommendations for pre-clinical development, clinical trial design, and labeling claims. Wound healing claims, for example, must be supported by valid scientific evidence establishing an improved incidence of wound closure or a reduction in time to healing.

In contrast to this rigorous pre-market review period for biologics, distributors of 361 HCT/Ps marketed for wound healing need only comply with the requirements for facility registration, donor screening, and good tissue practices. There are no clinical data requirements at all.

However, this situation's not limited only to wound care. Allograft distributors are also marketing injectable sheet and other forms of allograft-derived products through the Section 361 pathway for a variety of therapeutic purposes in other areas, such as orthopedics and general surgery. The minimalist regulatory scheme embodied in the Part 1271 is entirely appropriate for allografts that, in fact, meet the criteria set forth in Section 1271.10.

It is clear that Congress never intended that Section 361 would be used by commercial entities to circumvent the FDA regulatory review process to market manufactured allografts as medical therapies to treat, prevent, or mitigate a disease. But there are companies within the allograft industry who are systematically exploiting the jurisdictional criteria in Section 1271.10 to circumvent the conventional FDA pre-market review requirements applicable to other biological products.

Many companies are self-designating their products to Section 361 HCT/Ps even though the products do not, in fact, meet the criteria set forth in 1271.10. These companies have introduced to the market a host of human tissues claiming to interact with the body in complex ways. These products are processed in ways that are not minimal, are promoted for uses that fall far outside the realm of homologous use, and claim comparative or superior efficacy to FDA approved biologics and devices. This situation puts some

of our most vulnerable patients at risk and must not continue.

There are some who argue that these guidance documents incorporate new concepts or make new law and thus must, as a matter of law, be subjected to notice and comment rulemaking. In fact, however, these guidance documents simply synthesize and apply in examples the agency's longstanding positions as articulated in rulemaking preambles, untitled letters, and warning letters issued over the years, as well as decisions of the tissue reference group. The attempt to impose notice and comment rulemaking is a stalling tactic designed to delay enforcement action against products that should never have been on the market without pre-market review in the first place because they have more than minimally manipulated or being promoted for non-homologous uses.

In general, the drafts for minimal manipulation and homologous use are comprehensive and provide very useful guidance. Both guidances

would benefit from additional examples for both hard and soft tissue technologies to inform industry when developing products.

The draft guidances are a welcome step towards imposing order on an industry that has been operating more or less free from meaningful oversight. It is critical for the public health, as well as for the future of the regenerative medicine industry, that FDA finalize the draft guidances with all possible speed. Thank you for your time and attention to these comments.

DR. WITTEN: Thank you. Our next speaker represents RTI Surgical.

DR. DEURLING: Good morning. I'd like to thank FDA for holding this public hearing and for the opportunity to speak this morning. My name is Justin Deurling and I'm here on behalf of RTI Surgical. RTI manufactures and distributes HCT/Ps for use in life-enhancing orthopedic, spine, sports medicine, and surgical specialties procedures. As an institutional member of the American Association of Tissue Banks, we at RTI

echo the comments made by our colleagues at today's hearing and urge FDA to fully consider these prior to moving forward with finalizing any of these draft guidances. The continued availability and access to future lifesaving and life-enhancing treatments depends on the careful consideration of the potential impact of the agency's actions.

While RTI has numerous concerns with the draft guidances, I've elected to use my brief time at today's hearing to discuss the important role of sterilization and decellularization processes for ensuring the safety of HCT/Ps. And how the somewhat ambiguous nonspecific language of the draft guidance could block access to and inhibit the development of the safety enhancing processes, while vitally important donor screening and testing alone cannot guarantee the safety of HCT/Ps. Decellularization and sterilization processes enhance the safety of HCT/Ps by virtually eliminating the risk of donor to recipient disease transmission and implant

rejection, and are effectively deployed while retaining the relevant original characteristics of the process tissues.

Yet, by not specifically identifying these processes as not more than minimal manipulation in the draft guidance, the agency leaves the continued access to allografts utilizing these important processes up to interpretation. To illustrate this point, I'll briefly discuss one of RTI's tissue sterilization processes, but it is important that you keep in mind that similar sterilization and decellularization processes have been implemented by the various tissue banks across the country, improving the safety profile for the allografts they distribute.

The nonspecific language presently in the draft guidance could potentially jeopardize patient access to these safe implants. RTI's developed three tissue specific sterilization and decellularization processes as seen here. Today, I'll briefly focus specifically on the BioCleanse

process to illustrate these points.

The BioCleanse tissue sterilization process consists of gently oscillating pressure in the presence of chemical agents which gently profuse and completely penetrate the tissue. The combination of chemical agents removes blood and lipids and inactivates or removes pathogenic microorganisms. The BioCleanse process is validated through pathogenic organisms, including HIV, hepatitis B and C, bacteria, fungi, and spores. Repeated water rinses throughout the process remove debris and final water rinses remove residual chemicals, leaving the tissue biocompatible and retaining its relevant original characteristics. So that's what BioCleanse does.

Now, what doesn't it do? At a microstructural level, you can see the appearance of the tissue as unaltered compared to unprocessed tissue. The biomechanical and biochemical properties of BioCleanse processed tissue are also similar to unprocessed controls. Upon implantation, the biological response to

BioCleanse processed tissue is similar to autograft. So the tissue safety is markedly improved through the use of the BioCleanse process without impacting the tissue's utility for reconstruction, repair, or replacement.

In fact, through the use of sterilization and decellularization processes such as BioCleanse, today RTI's distributed more than 5 million sterilized biologic implants with zero incidents of implant-associated infection. And yet as written, the draft guidance does not acknowledge the important role of processes such as BioCleanse in ensuring patient's safety and eliminating the spread of communicable diseases by specifically designating sterilization and decellularization processes as not more than minimal manipulation.

Again, while important, donor screening and testing alone cannot guarantee the safety of HCT/Ps. In sterilization and decellularization processes, enhanced tissue safety by eliminating the risk of donor to recipient disease

transmission and implant rejection. Yet, the draft guidance as written does not recognize the importance and utility of these processes for preventing the spread of communicable diseases.

Therefore, RTI in alignment with AATB recommends FDA restate the list of processes that are considered minimal manipulation that was presented in the preamble to the original tissue rules and expanded to include both decellularization and sterilization using any validated technique, as seen here on this slide. Only through the use of clear, unambiguous language such as this can the agency ensure the continued availability of these safety enhancing processes. Thank you for your attention.

DR. WITTEN: Thank you. Our next speaker represents StemGenex.

DR. BRODY: My name is Steven Brody. I'm an M.D., Ph.D., and I'm the chief scientific officer at StemGenex. You know, my academic and scientific career began at Cambridge then continued at Yale and then it led to three years

of clinical research right here at the NIH. So for me this is a homecoming. While I was at Stanford, I co- authored a textbook with Robert Edwards, who received the Nobel Prize in Medicine in 2010.

As a reproductive endocrinologist, I have seen how the evolution of regulations have helped guide advances in in vitro fertilization. And in this context, my work in stem cell therapeutics is a natural transition. Thanks for the opportunity to comment on these four draft guidances. It is really a matter of public health, public safety and also public access to these stem cell therapies.

Now, adipose tissue contains cell types with nonstructural functions. We mustn't think of fat tissue as just adipocytes. It's monocytes, parasites, granulocytes, and, most important, the stem and progeny cells which have the capability of repair and regeneration. This is so important.

Now, let's focus on the stem and progenitor cells for a second. They have

immunomodulatory functions. They have cell signaling functions. They have hormonal functions and, again, they have the property to potentially repair and regenerate tissue, not just treat disease, but repair and regenerate tissue. On this basis, the fact that these cells have these properties, it is reasonable and it is warranted to view adipose tissue as both structural and nonstructural.

And finally, in accord with these comments, we must recognize that there are biological effects of fat on target organs and tissues. The most important thing is that fat isn't even meant to be structural in the human body. It's a repository of energy in times of caloric scarcity. It's not even meant to be a structural organ per se, although it plays a role in our society as a structural organ. But look at all the effects that it has on other tissues in the body. In fact, fat tissue's the endocrine and an immune gland, therefore, it really must be viewed as not just structural, but also

nonstructural.

Now, the question of minimum manipulation is an important issue. Now, if we use a GMP enzyme for recombinant DNA, no contamination, perfectly safe, and we take cells with specific biological characteristics. We use this enzyme to isolate the cells from the parent tissue which is harvested, there are no significant biological characteristics that are changed in these cells. And then in our model of giving them back autologously in a very safe manner.

Now, if we could expand the definition of minimal manipulation, this would help our patients have access to stem cell therapies. This is so important. Now, this timeline comparable to one of the other speakers that shows really the progression of the use of cellular therapies in medicine. And in fact, these lifesaving procedures are now considered standard of care, dating from blood transfusions, bone marrow transplants and other organ transplantation

systems.

Now, we have the advent of stem cells and stem cells have captivated the imagination of the scientific and academic communities. One of the reasons why I switched fields, it's a burgeoning field and there's no question it will impact every single aspect of medical practice.

Now, with this excitement comes responsibility, and with responsibility comes regulation. The American Association of Blood Banking, as listed here, has been successfully setting standards in cellular therapies for over 20 years. Accreditation by the AABB is based on the core principles of efficacy, scientific validity, and patient safety. The standards of the AABB, which were developed in the past, have been recognized both nationally and internationally. Furthermore, the AABB and the FDA collaborate on an ongoing basis.

DR. WITTEN: Excuse me. I'm afraid --

DR. BRODY: I believe this is the idea --

DR. WITTEN: -- you're going to have to wrap this up.

DR. BRODY: Thank you very much.

DR. WITTEN: Our next speaker represents U.S. Stem Cell Inc.

DR. COMELLA: Thank you. I'm Kristin Comella. I'm the chief science officer of U.S. Stem Cell. We are a publicly traded company, so I must remind you of the forward-looking statements. We have a comprehensive mix of products. We've been a company since 1999, and our focus has always been to bring stem cell therapies to patients.

I think this quote is particularly important today. All truth passes through three stages. First, it's ridiculed. Second, it's violently opposed. And third, is it accepted as being self-evident?

The re-implantation of autologous HCT/Ps is recognized in the regulations and during the same surgical procedure, this is considered the practice of medicine. And there are a variety of

different things that are recognized under this, including fat grafts, skin graft, bone marrow transplants, platelet rich plasma, tendon and ligament grafts, vascular grafts, hair grafts, and bone grafts. All of these procedures are considered surgical and they did not go through double-blind, placebo-controlled trials.

I want to focus on the comparison between bone marrow and fat tissue, and, in particular, something called stromal vascular fraction that a lot of people have been discussing today. The reason that bone marrow is accepted under a 510K is because there was preexisting technology to the 1976 amendments covering medical devices. Fat tissue does not have that same luxury because there was no preexisting technology. But why would fat and bone marrow be viewed separately? When you're taking cells from bone marrow, why is this different than taking cells from fat? And in particular, fat is a less invasive method of collecting and also isolating the cells with lower risks associated with it.

In addition, there are higher numbers of cells and stem cells and lower numbers of white blood cells which are inflammation creating in the fat tissue versus the bone marrow. So scientifically speaking, it makes zero sense that we'd regulate these two tissues in a different manner. Why would the FDA regulate our own body tissue and consider this a drug?

Who is responsible for paying for these trials if the FDA doesn't do it? Pharmaceutical companies typically cover the expenses associated with doing a double-blind, placebo-controlled trial. Because there is no drug to sell at the end of this because it's cells from your own body, no pharmaceutical company is going to cover these trials, so who is going to cover these trials if they're going to be mandated by the FDA?

In addition, why would the FDA regulate cells from bone marrow and fat tissue different? These are some images from our clinic where we treat patients. These are our medical practitioners who care very much about their

patients, and their safety and outcomes, and who have become, in some sense, disgusted with the medical system and some of the products that are currently available that are not making patients better. We need new options for patients.

The process is very simple. It can be done in under 60 minutes. A small sample of fat tissue is taken in a minimally manipulated process where the patient remains awake. There is no general anesthesia. The cells are obtained and can be administered back to that same patient.

We've trained over 600 practitioners throughout the world and in the U.S. who are doing these procedures safely. We have over 6,000 cases documented and when you consider some of our colleagues, there are tens of thousands of cases documented. If this was really a safety concern, there would be more than a handful of adverse events which are being reported. And that's all we have right now, just a handful out of ten thousands of patients. And there is no drug on the planet that has that kind of record.

Regenerative medicine is here to stay and it's continuously growing. We, as a field, have an obligation to bring these therapies forward. Patients have a right to make an informed consent decision about how they're going to use these treatments on themselves. They have a right to alternative therapies. We need more funding for these patient trials and the government should not regulate all bodies. I'm Kristin Comella and I will always stand up for patient rights. Thank you. (Applause)

DR. WITTEN: Thank you. There were three speakers who were not here at the time. Have they shown up? No.

Okay, in that case, I will call for questions -- or open into questions from the panel to the speakers. Any questions?

DR. ANATOL: I do.

DR. WITTEN: Okay.

DR. ANATOL: Okay, I have a question for the first speaker from Alliqua Biomedical. On your summary slide, you have a bullet that says

consideration of multitasking of human tissues and cells in both donors and recipients. Can you clarify what you mean by "multitasking?"

DR. SMIELL: I'm talking about in multitasking of human tissue; I'm talking about the matrix signaling that can happen from components of the structural tissue. Is that an --

DR. ANATOL: Thank you.

DR. SMIELL: Mm-hmm.

DR. WITTEN: Also, have a question for you from Alliqua Biomedical, maybe you could --

DR. SMIELL: I'm sorry. (Laughter)

DR. WITTEN: Sorry, I didn't catch you before. Thank you for your thoughtful slide presentation. I do have a number of questions, some of which are regulatory in nature, so they really are questions for us.

DR. SMIELL: Yes.

DR. WITTEN: But I'm just wondering if you, yourself, have the answers to some of these. For example, just an example, safety of added

processing or preservation agents. You're asking who determines it. So I'm not really asking you that, but I'm just wondering --

DR. SMIELL: Well, I --

DR. WITTEN: -- if you have any ideas along the lines, either for that question or as it relates to any of the other questions you asked in your slides?

DR. SMIELL: So bottom line, I do believe we need a process similar to the request for designation that does a review of all the processing steps, source of tissue and claims that wish to be made that would be mandated for everyone to go through prior to marketing tissue products.

DR. WITTEN: I see, so that's more broadly than just the answer to this question. Yeah, okay. Thank you.

DR. SMIELL: Yeah, I'm sorry.

DR. WITTEN: Okay, I have a question for the speaker from Johnson & Johnson which is, I'm just wondering, you made a number of comments

about what you thought should be subject to oversight or shouldn't be subject to oversight. And I'm wondering if you could map those two comments on the guidance documents themselves?

DR. SIEGEL: I'm sorry. Comments about what should or shouldn't be?

DR. WITTEN: You made some comments in your talk. I'm sorry I wasn't able to write the whole thing, but we'll get it on the transcript. But you made some comments about what you thought should be regulated differently than tissues, so like the operating -- the institute should be --

DR. SIEGEL: Oh, okay. Right, right, right.

DR. WITTEN: And so I'm wondering, like, if you would map two comments on the guidance document, what would you be saying exactly?

DR. SIEGEL: Well, yes. Specifically, I would say that while the guidance document creates a different standard for the same surgical procedure exception from the standard for minimal manipulation, and that's highlighted in footnote 4

and elsewhere in the guidance document under question 4 and in the last paragraph of the major section, that there isn't a good rationale for that difference. So, the exception is only eligible for products that are rinsed, cut, or cleaned. And I would suggest that other forms of minimal manipulation should also be eligible for the exception because should those products -- assuming those products are used for homologous use in the same surgical procedure, to regulate them not under 361; to regulate them under 351 -- I mean, to regulate them under 361 rather than to accept them would be to impose additional controls on their spread of communicable disease since that's what 361 does.

And as I noted, there are a need for additional controls on spread of communicable disease within surgical procedures and so I think that would be an unnecessary burden. The other area is to consider because of the intrusiveness of regulating in and inspecting operating rooms, even for more than minimal manipulation products,

where they can be adequately controlled through FDA regulatory control of the drug device or biologic used for the manipulation. Maybe a vector, maybe a growth factor, maybe a machine that processes that the FDA should consider applying the exception so that the cell -- the HCT/P itself does not require pre-market approval, but those uses of the device does, as I think that would be a more efficient and effective regulation.

DR. WITTEN: Thank you. I have a question for speaker number 10. I'm sorry, I'm not sure who was speaking from -- this was from LifeNet Health. Whoever spoke from LifeNet Health, I'm just wondering, there are comments about what isn't minimal manipulation, but I'm just wondering if there any examples that you can provide of what you would consider minimal manipulation -- more than minimal manipulation?

DR. MOORE: More than minimal manipulation. Examples of those --

DR. WITTEN: Not trying to put you on

the spot, so --

DR. MOORE: Well, this is the spot. It's a good place. (Laughter) That's where you want to be.

So more the minimal manipulation, I think that if you took, for example, some cellular therapies and took the cells, and expanded them up and -- a gentleman was saying putting a vector in there or something. You know, obviously, there's things you can do that would be more the minimal manipulation. Again, expanding cells and treating them in certain ways, I think you can cross the line and that would be a particular example.

DR. WITTEN: Okay, thank you. Other questions from the panel? Okay, well -- oh, okay go ahead.

MR. WEINER: I just had one question for Dr. Lallande, is that right?

DR. BRODY: (inaudible)

MR. WEINER: Sorry. If I understood your presentation correctly, I think you were focusing on minimal manipulation questions and I

was just curious --

DR. BRODY: Yes.

MR. WEINER: -- if you have any comments on how that ties into the --

DR. BRODY: I'm sorry?

MR. WEINER: I was just curious if you had any comments on how the analysis would shift toward -- if you're talking about homologous use, if you had any views on homologous use for stem cells?

DR. BRODY: I'm sorry, I didn't hear your question. Can you repeat again?

MR. WEINER: I was just curious if you had any thoughts on homologous use as for -- seriously it might be a logical continuation from what you were saying about minimal manipulation for stem cell sources, if you have any comment on it? If you don't, that's fine, on homologous use. What would be within balance or how the two connect?

DR. BRODY: I believe that the use of this type of enzyme -- the competent DNA-derived

enzyme really can be used whether it's homologous or non-homologous. What we like to believe is that the homologous use -- the definition of homologous use should be expanded because these cells don't function as structural tissues per se. And these cells are within fat tissue which are called structural, which, in fact, are not even biologically the correct terminology for their purpose in the body.

They're only for long-term storage of caloric energy in terms of biologic restriction and yet we're eliminating it to the concept of it's just structural tissue. But I believe it plays the right role if you use the right enzyme; if you use it in the right conditions, there is no alteration of the biological characteristics, so it would fit in those two useful categories.

MR. WEINER: Thank you.

DR. WITTEN: Okay. I have one last question which is for the RTI Surgical, speaker number 16, if you're still here? And this is just for some clarification of your comments. And

thank you for coming and commenting to the guide pieces. I just would like to know -- so your suggestion is that the guidances clearly call out sterilization methods as not more than minimally manipulative. But I'm just wondering is there something in the guidances that has raised this question? Or are you just making a suggestion that that should be included, also?

DR. DEURLING: It's simply a suggestion that improving the specificity of the document, especially for processes that are important to the safety of HCT/P as sterilization processes, that should be specifically called out as being generally not more than minimally manipulated, especially since it was already in the preamble to the original rules, so just basically restating it.

DR. WITTEN: Basically restating it. Okay, thank you. Okay, well I see we're ahead of time. If there are no more questions? I see we're ahead of time so perhaps we can have the break now. And maybe we can reconvene instead of

reconvening at 11:27, we convene at 11 and have -- oh, yes?

SPEAKER: Are members of the audience permitted to ask questions?

DR. WITTEN: We are not allowing questions from the public. I'm sorry.

SPEAKER: Okay.

DR. WITTEN: But if you have comments, please submit them to the docket. We would be interested in --

SPEAKER: Can we submit for tomorrow?

SPEAKER: Until the 27th --

DR. WITTEN: You can submit until the 27th --

SPEAKER: -- of September.

DR. WITTEN: -- of September.

SPEAKER: Okay.

DR. WITTEN: Yeah. Okay, so we'll have a break. I think we'll -- oh, okay. We're going to reconvene at 11:05. And we'll hear the FDA presentation at that time assuming my presenter is actually here.

SPEAKER: Yeah, he's here.

DR. WITTEN: Oh, good. Okay, thank you.

(Recess)

DR. WITTEN: Okay. Thank you. I'm just going to introduce, as I mentioned this morning, Dr. Steve Bauer, Chief of the Cell and Tissue Therapy Branch in the Division of Cell and Gene Therapies in the Office of Cellular Tissue and Gene Therapies at the Center for Biologics, Evaluation, Research. Dr. Bauer's going to provide a summary from the September 8th FDA workshop on Scientific Evidence in Development of Human Cells, Tissues, and Cellular and Tissue-based Products that are Subject to Pre-Market Approval. Following his talk, we'll take a break for lunch and because we're running a bit early, we're going to reconvene at 1:00 from the lunch break. So I want to make sure that everybody knows that 1 o'clock is when we're going to reconvene. Okay.

DR. BAUER: Thank you, Dr. Witten. On September 8th, FDA convened a public workshop

entitled Scientific Evidence in Development of HCT/Ps Subject to Pre-Market Approval. The purpose of the workshop was to identify and discuss scientific considerations and challenges to help inform the development of cellular therapies, including stem cell-based products. I am going to provide a summary of the meeting and present highlights of the presentations and scientific discussions.

The invited speakers and panelists represented a variety of stakeholder communities, including academia, the pharmaceutical industry, professional societies, and U.S. Government agencies. Materials from that workshop, including speaker biographies and the agenda, are available on the vaccines, blood, and biologics part of the FDA webpage. Transcripts will be posted there as soon as they are available. And we'd like to, again, thank all the workshop participants for the excellent presentations and lively, informative discussions.

We began the day with a keynote address

from Dr. Irv Weissman, director of the Institute for Stem Cell Biology and Regenerative Medicine at Stanford. He gave a keynote presentation highlighting many years of academic research that led to efforts to develop a stem cell-based product. Dr. Weissman's talk emphasized the importance of strong scientific evidence during development of a cell therapy.

Dr. Weissman emphasized that the term "stem cell" is often misused. The term is often applied to mixtures of cells that are not all true stem cells. A stem cell can be defined as a cell that divides to replicate itself into another stem cell, but also has the ability to differentiate into other cell types. What many people call stem cell transplants are, in fact, mixtures of cells that may or may not contain true stem cells. And Dr. Weissman suggested that the term "stem cell treatment" be applied only to purified stem cells.

After his keynote address, I presented FDA perspectives on scientific evidence in HCT/P development. I explained the applicable

regulatory pathways and the scientific review disciplines involved in oversight of these types of products. For cell therapy, scientific evidence is the key consideration at each stage of product development. Gathering of scientific evidence starts in the pre-clinical phase before any administration to humans. At this stage, scientific evidence is gathered to support safety of potential human study participants and to provide evidence to support the concept of how the product may work.

Next, scientific information that tells us what is in the product and shows that it is free from harmful agents is gathered. If the information is sufficient, the initial human clinical trials can begin. If early phase 1 clinical trials continued to indicate product safety, and phase 2 trials provide some evidence that the study products are working, confirmatory phase 3 human clinical trials can be conducted. If well-designed, scientifically rigorous clinical trials support safety and effectiveness, then the

product can be moved toward the market.

Science is the key consideration for characterization of the product for evaluation of pre- clinical evidence and for conduct, and analysis of the clinical trials. I described some of the key scientific knowledge gaps where progress would facilitate development of safe and effective cell therapy products. In terms of product characterization, the field would benefit from development of ways to measure cells that predict their biological properties related to clinical performance. I described an FDA regulatory science research project that we call the multi-potent stem cell or MSC Consortium.

MSCs are often called mesenchymal stem cells, but they are not a pure preparation of stem cells. The Consortium has shown that commonly used methods to characterize MSCs do not reveal the differences between MSCs grown for different lengths of time or isolated from different donors. The Consortium has developed quantitative methods that do reveal the differences among MSC

preparations in some ways to characterize some biological properties. These tools could improve manufacturing and characterization of MSCs and other cell therapy products.

In session two, industry and academia -- academic scientists presented their experiences in cell therapy product development. Speakers emphasized there should be a two-way flow of scientific understanding that comes from pre-clinical and clinical studies. This means that pre- clinical and clinical experience should feed back into the lab and inform manufacturing of the product. Careful analysis of the pre-clinical and clinical results can lead to significant refinement and improvement of cell products. One speaker emphasized how important it is to have a sound scientific understanding of the cell product. This knowledge can help assess whether manufacturing changes will have a positive or negative effect on the quality of the final product. Several speakers emphasized that understanding the mechanism of action of the

product can help to design better clinical trials.

After the two morning sessions one and two, there was a panel session with speakers from these sessions. The panel provided additional discussion around the points I already covered and also discuss two additional points. First, regulatory oversight provides a critical review that advances product development. Secondly, panel members also emphasized that existing FDA regulatory pathways including orphan designation, expanded access, and others could expedite clinical development.

In session three, which was the first session of the afternoon, we heard from professional societies which have an important role in the development of cell-based therapies. Speakers representing the International Society for Stem Cell Research, ISSCR, and the International Society for Cellular Therapy, ISCT, provided summaries of their professional society's positions on what they call unproven cell therapies. Both emphasize ethical and scientific

concerns arising from unproven cell therapies and stem cell tourism. Both societies have issued guidelines which emphasize the critical importance of scientific data in providing the ethical framework for clinical trials.

The speakers pointed out that patients may not always understand whether or not there is scientific evidence that supports the treatments they are choosing. Also, the patients may not understand whether or not they are participating in a clinical trial with appropriate oversight. The ISSCR representative discussed the role of FDA in the product development process as an important collaborator who maintained balance between participants, including scientists, patients, academics, and industry partners. A representative of the American Society of Plastic Surgeons and the International Federation for Adipose Therapeutics in Science stated that his society provides guidance on the use of fat grafting and stromal vascular fraction to its members, and these groups see scientific quality

is important to the field.

In the next session, two federal agencies described the support they provide in development of cell therapy products in accordance with their missions. A representative from the Department of Defense discussed the important initiatives and goals of DOD supporting regenerative medicine research to benefit injured members of the Armed services. A representative from the National Institutes of Health discussed the National Heart, Lung, and Blood Institute support of translational science for regenerative medicine products, including a clinical specimen and data repository, a web-based small biz hangout, the Partnership for Access to Clinical Trials, also called PACT, and the Progenitor Cell Biology Consortium and the Progenitor Cell Biology Translational Consortium.

The final session covered topics related to patient and society experience and expectations. Speakers highlighted societal expectations for development of novel products

emphasizing safety as an overarching principle and the important role of informed consent. The speakers noted that patient advocacy groups are important, but do not necessarily represent the point of view of all patients. A representative from the Foundation for Fighting Blindness highlighted the complexity of cell therapies for treatment of blindness and the importance of careful scientific characterization of various types of cell products.

He expressed concern that some cell products were not suitable or not sufficiently supported by evidence for treating blindness. The Foundation for Fighting Blindness recommends that all clinical stem cell therapies have convincing preclinical and clinical safety data for safety and efficacy, as well as FDA oversight. Dr. Albini, an ophthalmologist in Florida, discussed outcomes in patients treated for macular degeneration. Three patients with relatively functional vision received bilateral injections of autologous adipose-derived cells. All three

subsequently developed permanent vision loss in both eyes. According to Dr. Albini, all three patients mistakenly believed they were participating in a clinical trial.

Dr. Miller from Brigham and Women's Hospital at Harvard discussed a 66-year-old man who sought treatment for lingering effects from an ischemic stroke. He was reportedly given multiple different stem cell injections described as mesenchymal, embryonic, and fetal neural stem cells. At several different commercial stem cell clinics outside the U.S., he subsequently developed progressive lower back pain, paraplegia, and urinary incontinence. Magnetic resonance imaging revealed a mass growing around his spinal cord. A biopsy from this lesion indicated the cells were not from his body, but came from the infused cells. He then received radiation therapy, which helped temporarily, but now the mass is growing again.

After sessions three, four, and five, there was a panel session with speakers from the

earlier sessions. Discussion addressed the importance of protecting research participants, the need for clinical trials to be conducted with appropriate oversight and backed by sound scientific data. The panel also commented that the public can find a tremendous amount of information regarding stem cell treatments online. More should be done to make sure the online information is accurate and that there is adequate information for both physicians and patients.

This may be a role for professional societies and FDA oversight. Another point was that patients vary in risk aversion, so there's a need to build in more respect for patient autonomy while protecting patients from excessive claims. All panelists agreed that the products need to be safe and should be rigorously developed to identify which products are effective.

At the end of the day, Dr. Weissman summarized some of the key points from the presentations and discussions. One of the key themes of the workshop was the complexity of cells

and the importance of sound science in development, manufacturing, pre-clinical studies, and clinical studies of cell therapies. Professional societies discussed their concern regarding the use of unproven cell therapies and stem cell tourism and highlighted their recommendations for protecting the safety of patients and for developing effective treatments. Government support is key to innovation and progress of regenerative medicine.

FDA appreciates the thoughtful discussion and input from the presenters, panelists, and audience members of the workshop. We also thank you for your participation today. So we will now break for lunch and reconvene at 1 p.m. Thank you.

(Recess)

DR. WITTEN: We're going to get started again. I'd like to thank the speakers this morning for keeping to their allotted time. And for those of you who are speaking this afternoon who weren't here this morning, there's a timer and

when it turns yellow you have a minute left to wrap up your presentations. So that's how you'll know that you're close to the end of your time.

So we're going to start this session, Session Two, this afternoon with a presentation from a speaker from Boston College Law School.

DR. CHIRBA-MARTIN: Thank you, I'm MaryAnn Chirba- Martin. I'm a professor of health law at Boston College Law School. I also teach health law at NYU Law School, and I've taught also at Harvard School of Public Health. I received my doctorate in health policy and law and my master's in public health, also from the Harvard School of Public Health. I'm speaking as an individual healthcare regulatory attorney. I do not speak on behalf of Boston College, no academic would, and since I've never been paid or grant funded for my work in this area, I have no financial conflicts of interests.

I appreciate the presence of all of you and the extension of time to hear people discuss these matters. And I also appreciate the great

difficulty that the agency has in regulating in such a complicated area that's often ethically complicated and emotionally charged. I hope someday there's a larger conversation about improving or revising the 351361 regulatory framework, but today I'd like to focus on the impact of three draft guidances on the use of autologous adipose-derived stem cell therapies for nonstructural purposes.

I'd like to discuss the homologous use draft guidance, the adipose draft guidance, and the minimum manipulation draft guidance.

In 1998, the agency issued a guidance on changing general to intended use for medical devices. And it explained that the purpose of guidance is to enable the agency to make consistent and reasonable decisions. And I'm concerned as an attorney that this is not happening here and that the agency's actions would not survive judicial review.

First, the agency is required throughout its regulatory actions to regulate based on a

product's intended use. And by refusing to acknowledge the use of adipose tissues for nonstructural purposes, it is essentially disregarding a manufacturer's intended use in violation of its statutory requirements to do so. By law this would generate absolutely no deference from a court under chevron analysis.

Even if the court were to examine these actions -- and guidances can be evaluated by judicial review in certain circumstances -- even if they were to extend some level of deference, I still think these would fail as arbitrary and capricious. The draft guidances themselves acknowledge that adipose serves both structural and nonstructural purposes or at least they include structural and nonstructural components and the authorities the guidances cite in support also say that that has both structural and nonstructural purposes.

And yet the guidances go on to impose this rubric of evaluating adipose therapies only in terms of their structural use. This inevitably

makes the evaluation of minimum manipulation impossible because the evaluation of minimum manipulation depends on the original relevant characteristics, relevant to the intended use. And it forces adipose therapies to be wrung through a framework of evaluating structural use when the relevant characteristics are nonstructural. So, at a minimum I urge this court to extend the use of structural to include both structural and nonstructural.

Then the homologous use stat, draft guidance poses an additional concern with regard to the ability of fat to serve structural purposes. It states that fat can be used to fill the hollows of a woman's cheeks, it can be used to restore the shape of a woman's body, but it cannot be used to reconstruct a breast. And the reason is because the basic function of a breast is defined as lactation and adipose does not restore lactation. Restoring lactation is not a woman's concern.

It was not the concern of the Women's

Health and Cancer Rights Treatment Act, which said that breast reconstruction is medically necessary. It is unfair and illogical and arbitrary and capricious to leave a woman with few options for reconstruction, most especially in a foreign implant when a woman would be most unlikely to tolerate it.

I ask this court to, at a minimum, exercise enforcement discretion as it did with its FMT guidance in March 2014, decide not to enforce these guidances against individual practitioners who are using same cell autologous adipose therapies for nonstructural purposes, and explain why a breast is mainly a lactation organ and nothing else. Thank you. (Applause)

DR. WITTEN: Our next speaker is from Case Western University.

DR. CAPLAN: Hi, my name's Arnold Caplan. I'm a professor at Case Western Reserve University in Cleveland. And I'm not speaking for the university, I'm speaking for myself as an individual.

In the late 1980s, I gave the term "mesenchymal stem cells" to a cell which I was able to isolate from bone marrow, put into culture, and expand in culture. That term is wrong, and I apologize for calling it a stem cell. It is not a stem cell. The assumption was that this cell was part of the stroma of marrow. The cell is not a part of the connective tissue or stroma of marrow. It is a perivascular cell. And as a perivascular cell, it has a function only in cases of inflammation or injury.

In this case, this cell comes off the blood vessel and does two things. From its front it secretes a curtain of molecules which stop your overaggressive immune system from surveying the damaged tissue behind it. And from the back of the cell, it secretes a different group of factors which actually allow the tissue behind it to regenerate in a slow and unscarring process. This, therefore, is a cell which is medicinal in its function and because I have such a delicate ego, I've written an article which asks my

colleagues to continue to use the MSC nomenclature, but I've renamed this cell a medicinal signaling cell. And so, therefore, when I lecture I beg the audience to not use the stem cell nomenclature. Having said that, I want to address two points of the guidance documents.

Number one, everything I've just talked about is paracrine activity of cells. And so I would state that almost every tissue of the body is itself paracrine. Fat in particular has an absolutely essential paracrine activity as a tissue; and so, therefore, if you transplant or transfer fat from one tissue to another, you're taking advantage of its paracrine activities, which are not covered whatsoever, as the last speaker pointed out, in your guidance documents. And so, therefore, I would suggest that the guidance document could be augmented by talking about clinically homologous use. And so, therefore, a fat transfer to my knee, to my elbow, to my shoulder are all comparably clinically relevant and could, therefore, produce a paracrine

and/or clinically relevant activity as some published studies have shown. So this is suggestion number one.

Suggestion number two is that the guidance documents and the emphasis of the meeting on Thursday was to try to put at rest the illegal or irrational or unsupported use of cell-based therapy. My suggestion in this regard would be a registry. A registry which puts the -- of course, protects the patient's name and identity, but puts the clinical symptoms under which they're being treated and outcome parameter lists, sequential outcome parameters so that one could determine whether a particular therapy was effective or not effective. If that web, if that registry was in real time on a publicly accessible website, then we could determine just as patients, whether a particular doctor's office was producing clinically relevant results from any one of these therapies. I want to state unequivocally that this has been in practice for over 25 years for bone marrow transplantation, which the FDA

supports and allows. So it seems to me that the FDA likewise, in helping to make sure that efficacious, clinically efficacious technologies are being used, should support also a registry for other cell-based therapies and/or tissue transfers. It's important I think that these guidance documents are based in science and in the reality. And this paracrine activity is one of the most important, and I, of course, will honor any decision this panel will make and help enforce it.

Thank you.

DR. WITTEN: Our next speaker is representing the Indiana University School of Medicine.

DR. MARCH: Hi, I'm Keith March. It's a great pleasure to be here. Just as stated by the prior speakers, of course, I am representing the opinions that I can best offer, and I hope that they're helpful. I can't actually represent the entirety of the university, Indiana University.

My M.D. is in cardiology, expressed in

cardiology in terms of practice with patients, which I still do, and my Ph.D. is in protein biophysics. I direct the Vascular and Cardiac Stem Cell Therapy Center at Indiana University. And this has really grown from our activity that was involved in adipose stromolar stem cells. I'll still use that terminology even though Dr. Caplan has offered some other terminologies -- work that we began in the 2001 time frame and since then, we've been able to define that those cells were very active in angiogenesis, vasculogenisis, and support of the parenchyma. And we've also been able to define that the adipose stem or stromal cell is located in a periendothelial position around the vasculature, as was offered in a broader sense by Dr. Caplan for MSCs throughout the body. This understanding leads us to be very interested in the concept that these cells represent a subset of a body-wide portfolio of mesenchymal stem or stromal cells or, in fact, medicinal secretory cells.

And as such, I think one concept that we

would like to introduce is that we consider the notion of a functional homology rather than an anatomically sourced homology. And just as he mentioned, I think this nicely dovetails that vascular and tissue support that these cells naturally undertake physiologically is what they're often being used for, let's say in the context of skeletal or heart muscle ischemia; also in the context of renal ischemia, the nervous system, intestinal, and eyelet based ischemia. So as you can see a wide range of topics, if you will, or organs, where a target is appropriately considered to be the subject of a homologous function of these cells, and I think that's maybe a useful concept to consider.

Well, all the work we've been doing with the adipose stem cells led us to be very interested in cell therapy trials more broadly. We've had the privilege since 2012 to participate as one of the seven members in the United States of what's called the Cardiovascular Cell Therapy Research Network, which is supported by NIH.

Very privileged and thankful to be one of those members, and also I had the chance to be the Clinical Network BSMB chair for several years before we became a member of that network.

So as such, we've had the opportunity to participate in the planning or conduct of seven clinical trials involving either bone marrow or SVF, stromal vascular fraction. And all of those have been regulated in context with the development and discussion with the FDA. And we very much appreciate and have found the CBER guidance and help through those discussions to be enormously useful. So everything we've done is in either the IDE or IND environment. And in fact, we have four more that we're preparing with IDEs involving SVF or other indications.

So from that perspective or history, I would like to then move to some comments relating to the draft guidances touching on SVF and ASCs. The one I've already made in particular is about the functional homology, and I think that relates to the notion of what is a homologous use.

The second I'd like to make rests on a thought about history and patient autonomy. Bone marrow transplant is of great interest to all of us and as is cord-blood transplant. Those began to be developed in the '70s and '80s and as a mere cardiologist, I thought it important to talk to some real HEMONC colleagues. So I've talked to several about this topic of bone marrow and cord-blood transplantation who allowed me to cite them actually.

Ian McNiece, who's been involved in the bone marrow field for about 35 years and was a director of the bone marrow transplant laboratories at Johns Hopkins followed by the University of Miami, followed by MD Anderson, as well as Joanne Kurtzberg, who's here in the audience, and Pat Lara, our home, at Indiana Cell Cancer Center Director. And all of them have declared that if the regulatory environment back in those times were more similar to how it is now, we may not in fact be able to have had the opportunity to see, say, a million bone marrow and

cord- blood transplants have occurred, which I believe was the number I saw cited in 2013, with of course many of those people benefitting significantly.

And the reason for that is that in those early transplantation efforts we didn't know much about HLA. And dozens, if not hundreds of people died as a consequence. However, those findings about HLA were in fact critical to the advancement of the field.

And so I think a consideration about risk-benefit and where we are with the bar, if you will, that's placed for entry into human trial and learning not only about efficacy, but also about safety, needs to be considered. Some have said that if in fact we were in that domain back then, we may not have bone marrow transplant at all. So I think we need to think about whether some kind of relaxation or moderation of restriction might allow more work to be conducted and offer more opportunities in the United States. And I would totally agree with the prior comments from Dr.

Caplan about the field needing a registry, such that participation in clinical trials be actually brought into a mandated situation so that registry and data can be brought forward.

The last comment that I have is a regulatory one, and that is, some of the clinics that we are, I think, uniformly trying to regulate in addition --

DR. WITTEN: Excuse me.

DR. MARCH: Yes.

DR. WITTEN: I just want to mention, I appreciate your comments, but you need to be mindful of the time limitations.

DR. MARCH: Okay.

DR. WITTEN: Okay.

DR. MARCH: I think then I'll take this last point, and I will hold it for another discussion if we want to. I think the main points I brought forward as best as I can and I appreciate your time. Thank you.

DR. WITTEN: The next speaker is from Wake Forest University School of Medicine.

DR. ALICKSON: Hello, my name is Julie Alickson and I'm the director of the Regenerative Medicine Clinical Center at Wake Forest Institute for Regenerative Medicine. I've been in the field for about 25 years, cell therapy regenerative medicine, and now lead the Clinical Center where we work with cell therapies, tissue engineered organs, bio-materials and devices. So I've been pre and post good tissue practice regulations and I'd like to comment on two of the guidance documents. I'd also like to thank FDA for allowing me to speak in a public forum and along with all the others to be able to help to form the final guidance documents that you're working on.

So I'd like to comment on the guidance documents that are associated with the 1271 homologous use of human cells, tissues, and cell and tissue-based products that was published in October of 2015. And it starts out by the first question, what is the definition of homologous use? And so I'm just going to kind of lead you. I have a couple comments and recommendations for

this guidance document, and so it talks about homologous use means repair, reconstruction, replacement, supplement of the recipient cells and tissues with an HCT/P that performs the same basic function, including cells or tissues. And we're talking about the cells that are identical, either to the donor cells and tissues or the recipient cells that may not be identical to the donor.

They go back with number three talking about the same basic function in the definition of homologous use, the same basic functions considered to be those basic functions of the HCT/P that performs in the body of the donor, which when transplanted, implanted, infused, transferred would be expected to perform in the recipient. The recipient to perform all basic functions, it performs in the donor in order to meet the definition of homologous use.

However, to meet the definition of homologous use, any of the basic functions that the HCT/P is expected to perform in the recipient must be a basic function that the HCT/P performs

in the donor. So the draft guidance goes on to talk about several different examples that then can be either homologous or non-homologous use, and I'm looking at 3.4, the basic functions of amniotic membrane, including covering, protecting, saving as a selective barrier for the movement of nutrients between the external and in utero environment.

Amniotic membrane is use, they give the example of bone tissue replacement and they are saying that this is not homologous use, which I agree with, but I'd like to recommend and offer my comments that possibly they include when amniotic membrane is used as a selective barrier to retain fluid, potentially over wounds or some other environment that it could be considered a homologous product.

The other guidance I'd like to comment on is minimal manipulation of human cells, tissues, and cell-based products. And this talks about the definition of minimal manipulation -- sorry, the minimal manipulation talking about

structural tissue. And it means that the HCT/P does not alter the original relevant characteristics of the tissue relating to utility, and for cells that the minimal manipulation does not alter relative biological characteristics.

If you go down to example 7.1 of the amniotic membrane, original relevant characteristics of the amniotic membrane serve as a barrier generally for the tissues physical integrity, tensile strength, and elasticity. So there's two examples under there, and I'd like to recommend that there be a third example.

The first example talks about a minimal manipulation of the amniotic membrane that's mechanically and chemically processed as a decellularized amniotic membrane. The second example talks about the manufacturer grinds and lyophilizes the amniotic membrane and packages that as a powder, and this is more than minimally manipulated. I'd like to offer an in-between comment, and if we could put another example in there that the manufacturer that only lyophilizes

and freeze dries that amniotic membrane and packages it as sections to maintain that structural integrity is considered minimally manipulated as the dehydration process is just preserving that tissue. And it would be, if it's used as a membranous barrier such as it's used as the amniotic membrane.

I'd also like to say that regenerative medicine is a game-changer, so I'm hoping that we'll have the opportunity to move some of these lower risk products forward for people and their attention. I'd like to thank the FDA in allowing us to speak, and thank you.

DR. WITTEN: Thank you. Our next speaker is from Alston & Bird.

MR. SCHEINESON: Good afternoon. Forgive me for reading this, but five minutes isn't a very long time. Thank you for the opportunity to speak directly to my former FDA colleagues concerning these guidance documents. I understand this is a bit of a marathon for everyone. Detailed comments will be submitted

electronically with legal authorities.

My name is Mark Scheineson. I head the Food and Drug Practice in the Washington office of Alston & Bird. As a practicing FDA lawyer for over 35 years and a former FDA associate commissioner, I've worked with dozens of clients on constructive ideas to help advance medical innovation. I also represent the bipartisan policy center, which will speak in session three in its panel of cell therapy experts.

Together, they seek to modernize the Food, Drug, and Cosmetic Act to create a practical statutory pathway tailored to the unique attributes of cells and tissue-based therapies rather than relying exclusively on the patchwork of regulations and guidance. Because I've only five minutes to speak, probably now four, I will get directly to the point and will likely speak way too fast.

From the perspective of clarifying the agency's discretion or ambiguity in its application of terms used in 1271 and promoting

consistency, the draft guidance is welcome and appreciated. However, my colleagues and I believe that these guidances miss an opportunity to recognize the revolution in cell therapy that surrounds us.

While none of the speakers want to sanction quackery, there are unsafe clinical practices. FDA adopted language and examples that are even more conservative and restrictive than its actual application of these rules in review of existing products.

This might have been okay in 2001, when the 1271 rules were initially promulgated, but not in 2016, when the entire world has taken notice and expedited use of regenerative characteristics of patient cells based on thousands of published clinical studies. It is also not okay because of the existing regulatory paradigm, where if narrow cell or tissue use is not regulated by 1271, these uses are thrown across a Grand Canyon into the BLA or PMA drug and device delivery pathway. As you know best, that pathway takes an average of 12 to

15 years of development time and 200 million to a billion dollars in financial resources. Our top three suggestions to revise these draft guidances in the finals are these.

Number one, please don't ignore the discretion and regulatory tools you possess to foster innovation while protecting patients. These guidance documents all slam the door shut on the use of stem cells, which even in the narrow circumstances need to proliferate and differentiate to work.

Just as a generation of hemopoietic stem cells from cord blood have eliminated the need to extract bone marrow matches in treating blood cancers, why shouldn't panelists have the right to use their own stem cells for simple, orthopedic or cosmetic uses now if responsible, registered and licensed clinics observe all the protections inherent to 1271?

Number two, guidances are the most helpful if they contain specific examples, but the examples in these guidances are the most narrow

possible: homogenous skin grafts, heart valve replacements. My practice has, for example, seen FDA allow use of amniotic tissue to treat corneal erosion in the eyes as homologous under 1271 and other far more reaching examples. Why can't these types of cutting-edge examples be included in these guidances?

Third and last, most alarming is that FDA proposes to artificially limit the use of adipose stem cells and many others by reference to the underlying characteristics of the tissue in which those cells are located. Examples, structural support or padding and cushioning against shock in fat tissue. This approach minimizes the tools FDA gave itself in the plain language of 1271.3(f)(2), definition of minimal manipulation.

Cell manipulation as defined in a section of the regulation separate from structural tissue is allowing processing that does not alter the relevant biological characteristics of the cells themselves. FDA inextricably adds to the

cells the unrelated requirements of structural tissue in 1271(f)(1), where the processing can't alter the tissue's utility for reconstruction, repair, or replacement. If the product is a cell itself and not a cellular tissue and the cells possess the biological characteristics to divide and differentiate, it should be irrelevant that the cells were found in (inaudible) tissue and violate the regulation.

Formal written comments will include many other constructive suggestions. The regulated community needs bright lines. Thank you for your continued assistance.

DR. WITTEN: Thank you. Our next speaker represents Navigant Consulting.

DR. O'SHEA: Thanks for having us here. I'm Suzanne O'Shea. My comments today are based on my long experience as an FDA employee dealing with these issues and working in private practice for the last nine years with a number of tissue manufacturers. My comments are my own and do not represent the views of any client or my employer.

And I have five quick points to make today.

First, the draft guidance on minimal manipulation introduces the concept of main function for the very first time. The concept does not appear in 1271 or in any preamble to any proposed or final regulation. The draft guidance cites page 26749 in the preamble of the May 14, 1998, proposal for the assertion that the main function of the HCT/P in the donor determines which definition of minimal manipulation applies. However, the phrase "main function" is never used in the proposal. The closest phrase on 26749 is "basic function or functions," which is to be used in the context of determining homologous use. Creation of an important new concept cannot be done through guidance.

I request that if FDA wishes to pursue the main function concept, it do so through notice and comment rulemaking.

Two, the draft guidance on minimal manipulation provides FDA's unilateral conclusions on whether tissues are structural or

nonstructural. The guidance process does not provide sufficient opportunity for industry and academia to provide input into the classification of tissues as structural or nonstructural. I recognize that comments may be submitted to the draft guidance, and I do appreciate this public hearing.

However, FDA is under no obligation to articulate a response to comments submitted to a draft guidance or to explain its reasoning. I request that FDA's classification of tissues as structural or nonstructural be based on articulated reasoning that fully takes into account the views of industry and academia through notice and comment rulemaking.

Three, the draft guidance on minimal manipulation ignores the reality that some human tissues have both structural and nonstructural functionality in the donor. I recommend that FDA expressly acknowledge the full range of functionality of human tissue in the donor, including the reality that some tissues have

structural and nonstructural functionality.

As a specific case in point, FDA stated in a 2001 designation letter that amniotic membrane has nonstructural anti-scarring, anti-inflammatory functionality in the donor. FDA now says in the guidance document, without any explanation of why it has changed its mind, that amniotic membrane is only structural. I recognize that a designation letter is intended for a specific product and that may not be applicable to similar products. However, a scientific conclusion about the functionality of a tissue in the donor cannot vary based on the use of the product or the tissue in the recipient.

Number four, the draft guidance documents on homologous use explicitly relies on the classification of tissue as a structural or nonstructural to identify acceptable homologous uses. In creating the homologous use regulations, FDA considered and specifically rejected different definitions of homologous use for structural and nonstructural tissues. By importing the concept

of main function into the analysis of homologous use, FDA is limiting the range of acceptable homologous uses, contrary to current regulations.

Number five, FDA has applied the definition of minimal manipulation inconsistently. FDA has acknowledged that micronized bone is a Section 361 product when intended for use as a bone void filler, even though micronization self-evidently alters the strength and compressibility of bone.

It must, therefore, be the case that FDA has concluded that the strength and compressibility of bone are not relevant to the bone's utility as a bone void filler. On the other hand, FDA has concluded that micronized amniotic membrane is more than minimally manipulated when intended for anti-scarring, anti-inflammatory uses because tensile strength and elasticity are altered. Tensile strength and elasticity are not relevant to the utility of amniotic membrane for anti-scarring and anti-inflammatory uses. FDA has never explained

this discrepancy, and I request that FDA provide a scientific explanation for the difference. Thank you. (Applause)

DR. WITTEN: Thank you. Our next speaker is from OrthoKinetic Technologies.

DR. FERRARA: Good afternoon. I'm Dr. Lisa Ferrara and I'm president of OrthoKinetic Technologies and Testing Technologies, and I'm here today to give my independent expert opinion that tensile strength and elasticity of tissue is not altered by cutting the tissue into small-sized particles. My disclosure is I own OrthoKinetic Technologies and Testing Technologies. They're ISO certified fee-for-service companies.

The FDA draft guidance on minimal manipulation defines minimal manipulation as shown. In an example, FDA applied that definition to amniotic membrane that had been micronized, concluding that the micronized amniotic membrane is not minimally manipulated because the micronization process results in a loss of tensile strength and elasticity of the original tissue

related to its utility to function as a physical membrane.

OrthoKinetic Technologies was one of the independent testing firms that conducted the mechanical testing on multiple-sized amniotic membrane samples to determine if micronization of the amniotic membranes result in altered tensile strength and elasticity. My purpose for being here today is to discuss these results of that testing and to give my independent expert opinion that tensile strength and elasticity of a tissue is not altered by cutting the tissue into small particles.

Therefore, the objective of this study was to independently evaluate the dependence of size on the material properties of the amniotic membrane. As a background and as an engineer with a very strong background in tissue and test development and interpretation, I've spent many years testing thousands of human and animal tissue samples for the assessment of both the material and the structural properties.

For today's purposes, the main point of that is that the tensile strength and elastic modulus are material properties used to characterize the tissue. As explained in the next slide, material properties are independent of the size of the tissue as size is factored into the strength and elastic modulus calculations.

To give you an example of this, this slide demonstrates how the size of the tested tissue specimen is used to calculate the material properties of the tissue and why material properties are independent of size or configuration. The material tensile strength of a tissue is measured at the point of tissue failure and is expressed in terms of stress. Stress is proportional to the force applied for the cross sectional area to which the force is applied.

In the first example, a hundred newton force is placed across one millimeter squared area across the tissue, resulting in a stress of a hundred megapascals. In the second example, 200 newtons is placed across a 2 millimeter squared

area of tissue, and the stress again is a hundred megapascals. The material tensile strength will be the same regardless of tissue size based on these basic engineering principles.

The same principle applies to elastic modulus. The force measurement is measured in stress and the deformation is measured in strain. Strain is the relative change in length compared to the original initial length. The elastic modulus is the stress divided by this resulting strain. Therefore, a change in test sample size will be normalized by the results in stress and compensated for by the results in strain and the elastic modulus remains the same regardless of size.

With that background I'll discuss briefly the testing or the kinetic testing did on the amniotic membrane tissue. The methods involved obtaining samples of amniotic membrane, cutting them into different widths or different groups of widths. And at the time I performed the tests, OrthoKinetic technologies was not aware

that two other independent test labs were conducting the same testing in the same fashion for tensile strength and elastic modulus. For tensile testing the ultimate strength was measured and with consistent gauge length of 15 millimeters was used for each sample of different widths. Each sample was pulled to failure at a consistent rate and the membrane thickness was measured before and at the site of failure after testing.

These slides show the results, not only of what OrthoKinetic testing had conducted, but also the other two independent test labs. The upper right graph represents the results conducted by OrthoKinetic testing and the other two are the results from the other labs. The scatter plots for all three labs were similar with respect to the linear trends and scatter patterns and no significant difference was noted between widths.

The elastic modulus was tested in the same fashion and was determined from the stress and result and strain of each sample. Again, similar scatter plots, my apologies, similar

scatter plots were shown, similar linear trends, and again there was no statistically different between the samples for sample width and between laboratories. All three found no statistically different results for tensile strength and elastic modulus.

In conclusion, the results obtained in the study for all three laboratories have been presented in engineering parameters that are conventionally used to characterize material properties. The three independent studies all show there was no statistical difference in tensile strength or elastic modulus, and that the scatter patterns were all the same regardless of size.

Thank you for your attention.

DR. WITTEN: Thank you. Our next speaker is from Parenteau BioConsultants.

DR. YOUNG: Good afternoon. I am Dr. Janet Hardin-Young, co-founder of Parenteau BioConsultants, which provides scientific and regulatory consulting services with a focus on

cell-based therapies. I appreciate the opportunity to address certain important issues raised by the draft guidance documents under discussion, which will potentially provide much needed regulatory clarity in a space that has previously received insufficient attention.

I will focus my remarks on the concept of intended use. As a threshold matter, the purpose of agency guidance is to clarify existing regulation and FDA cannot and should not introduce new regulations via guidance. Despite objection to the various ways the guidances incorporate the concept of intended use it is, of course, not new.

The regulatory status of virtually every product under FDA's jurisdiction turns on the use for which its distributor intends it. In the concept of HTC/P specifically, the idea that the degree of regulation to which a tissue is subject would turn on its intended use has always been a bedrock principle of the risk-based approach that underpins Part 1271. Section 1271.10 incorporates the concept of intended use most notably in the

requirement that Section 361 HTC/Ps must be intended for homologous use.

When the regulatory scheme was conceived, the rationale for this requirement was that homologous use products can reasonably be exempted from pre-market review because a tissue's behavior for homologous use is readily predictable.

By contrast, products not intended for homologous use require pre-market review because clinical trials are necessary to establish the behavior of cells and tissues for each use. Nevertheless, today the market is crowded with products for which non-homologous unsubstantiated therapeutic claims are being made but are virtually unregulated.

A striking example is provided by skin and amniotic tissues base allographs, products marketed as wound treatments, where the validity of most of the claims being made is far from self-evident. The distributor of these products typically announce that the claims are supported

by clinical data. However, the studies are often underpowered, scientifically flawed and unlikely to meet FDA standards for valid scientific evidence.

Finalizing the draft guidance on homologous use is crucial because it will clarify for industry what is and is not permissible in the Section 361 HTC/Ps and will after, also, make enforcement more straightforward.

Historically, FDA has applied the concept of intended use in the minimal manipulation context. Finding that a particular process may be minimal for a tissue that is intended for one use, but not minimal for a tissue when it is intended for a different use. The minimal manipulation guidance has been criticized for introducing the supposed new concept of main function into determinations of whether a tissue is structural or nonstructural.

The reality is that FDA has been applying this concept to minimal manipulation determinations for almost 20 years. When FDA

proposed part 1271, the agency stated, "FDA recognizes some products may have both systemic and structural effects, but intends that a product's primary effect to determinative."

The term "main function" may use a new word, "main," instead of "primary," but the concept is well established and from my perspective makes a great deal of sense. For example, in the context of wound healing where allographs are promoted for the ability to improve the speed and quality of healing by interacting with the wound at the cellular level, the potential impact of various processes, processing techniques is much greater than the impact of these same processes when the tissue is intended as a wound covering which is merely a physical function.

In conclusion, I'd like to emphasize that wound healing products are targeted at a particularly vulnerable, chronically ill population. I'd like to urge the agency to move quickly to finalize the guidances, retaining an

approach that protects the public health and encourages innovation by providing meaningful clarity to the boundaries set forth in Section 1271.10.

DR. WITTEN: Thank you. Our next speaker is from the California Stem Cell Treatment Center and Cell Surgical Network.

DR. LANDER: Thank you very much. I'm Dr. Elliot Lander. I'm a urologic surgeon, co-founder and co-medical director of the Cell Surgical Network. The Cell Surgical Network represents over 400 physicians participating in nearly 100 multidisciplinary affiliated clinics in the U.S and around the world. Since 2010, CSN affiliates have performed over 5,000 procedures under IRB protocols using our standardized same-day cell surgical procedure with autologous SVF.

Our patients receive proper preoperative IRB informed consents and afterwards safety and efficacy data is collected online. Our data has been submitted for peer review publication and

also to the FDA. It is safe. There have been no deaths, infections, emboli, or any severe adverse events related to cell therapy. It works and improves many conditions where cellular repair is necessary.

While collecting investigative data, we provide cell therapy for our patients in a low-risk, cost-effective, and transparent investigational manner. Often at reduced rates, even for free, we're making regenerative medicine available to Americans today through our SVF outpatient procedures while we continue to gather data helping us to improve and advance patient care. This is the reason we became physicians.

While statements are frequently made claiming that such cell therapies are not FDA approved nor such clinics performing them regulated, let us remember that the practice of medicine is already heavily regulated by state medical boards, hospital peer review committees, plaintiffs' attorneys, and malpractice carriers.

But these regulations we address today

were born out of a congressional mandate to the FDA to prevent the introduction, transmission, and spread of communicable disease. With jurisdiction over drugs and devices, the FDA has now tried to define when our body parts come under their authority by considering federal rules based on fat being only a cushion, disregarding the science of what we know about fat.

Technically, with the contemplated rules the FDA would have broad sweeping jurisdiction over many traditional surgical procedures that don't strictly follow the new guidelines. We support guidelines giving the FDA the proper authority to ensure that we do not risk introduction of communicable disease from outside sources. However, rules should not be used to infringe on a patient's right to surgical options using their own autologous tissue. Do we really want artificial and scientifically arbitrary guidance rules to dictate the course of any surgical procedures that violate the proposed list of exemptions?

To date there has never been an FDA-approved surgical procedure. Further, same-day surgical procedures providing autologous cell therapies by their very nature are not fully closed systems and they can never be held to the same standards as a pharmacologically produced product.

Medicine has historically been advanced by the wise tradition of allowing physicians to use any FDA- approved drugs and devices in any way they see fit to advance innovation and help their patients. While some oversight might be prudent, guidance document language should be reasonably flexible for physicians and their patients, doctors should avoid irresponsible advertising and labeling claims not supported by data. And state medical boards and a variety of agencies are already in place to counter deceptive advertising.

CSN has endeavored to provide a transparent platform to gather real data. Our database registry system can be recapitulated or licensed by regulators as a model for the ethical

advancement of regenerative medicine. Reputable clinics will be able to easily comply with the registration process. Such transparency would only serve the public by helping us advance protocols that work, eliminate ones that don't, paving a path for more controlled clinical and laboratory validation studies in the future, but creating artificial and contrived rules that impact an entire nascent field of autologous SVF therapy will have unintended adverse consequences that will have epic ramifications. The FDA will be inadvertently selecting technology winners and losers that have little to do with safety and efficacy and more to do with the semantics of guidelines proposals.

The FDA will be complicit in criminalizing certain practices of medicine that are greatly supported by the American public, despite a recent smear campaign intended to marginalize a new way of healing patients. Every day our network team and the hundreds of doctors we do research with in the U.S and around the

world are seeing things that we were told were impossible in medical school. If this wasn't real and safe, we'd all go back to our previously successful practices, and autologous cell therapy would just simply fade away. Clearly that's not the case. Let patients and doctors decide. Let not special interests attempt to manipulate our distinguished regulatory agencies under the guide of protecting society. Thank you very much.

(Applause)

DR. WITTEN: Thank you. Our next speaker represents Celebration Stem Cell Center.

DR. BADOWSKI: Thank you for allowing me to address the panel today. My name is Michael Badowski. I'm a researcher who has, among other things, been working on the cells and tissues of today's topics since 1999. I currently serve as laboratory director of Celebration Stem Cell Center in Arizona, involved in cord blood stem cells and adipose tissue cryopreservation and as operational director of the University of Arizona Health Sciences Bio Repository.

As a researcher and a businessman involved in the use of human cells and tissues and on behalf of Celebration Stem Cell Center, we respectfully submit to the FDA to reconsider several points published in previous draft guidelines. We hope that, one, the FDA would broaden the definition of adipose tissue to include structural and nonstructural uses to better reflect the variety of effective clinical applications; two, allow the nonstructural use definition to more clearly determine homologous use; and three, refine and clarify the same surgical procedure exception.

Currently, the FDA utilizes the terms structural and nonstructural under 1271.10(a). It would support better outcomes for more clinicians and researchers if adipose tissue was not cataloged merely as structural. Changing the classification of adipose tissue to include both structural and nonstructural purposes would more accurately account for the intended use. And this concept of intended use is at the heart of the

rules that we would hope the FDA to adopt in regard to adipose tissue specifically in HCT/Ps in general. Adipose tissue can be defined as connective tissue consisting of a variety of cell types performing a variety of functions.

But because it's connective tissue in general, it provides support and structure to the body, FDA currently considers connective tissue including adipose tissue to be solely structural. Currently the many nonstructural functions have thus far been not sufficiently addressed.

Some examples for your consideration are: adipose tissue has critical function of energy storage which is not a structural function. More specifically, brown fat not only stores energy, but has an important role in using these stores in regulation of body temperature. Adipocytes store triglycerides and lipoproteins. These are critical chemical feed stocks for synthesis of cells in general and largely apply to erythropoiesis.

Important precursors such as forms of

cholesterol are also stored in adipocytes. Proper levels of these molecules have a profound effect on hematopoiesis. A great many adipokines are produced in the adipose tissue making it an important paracrine and endocrine organ. And perhaps most importantly, adipose-derived mesenchymal stromal cells have shown to be an important player in wound healing. All these examples are well known to the community and are all nonstructural. Furthermore, keeping adipose tissue listed solely as structural, make both the determination of homologous use and determination of the same surgical procedure more difficult.

Currently, the definition of homologous use requires that the tissues serve the same basic function in the recipient as in the donor. However, as I've just listed many nonstructural uses, they would not only apply for the homologous use exception because adipose is still defined as structural.

This is problematic because the use would fit all other qualifying descriptions as

homologous. The FDA has previously stated as part of the same surgical procedure exception that HCT/Ps remain in their original form. However, the Q&A published in October 2014, and other statements by the FDA leave ambiguity regarding the original form of HCT/Ps.

One might begin the conversation regarding HCT/Ps by acknowledging that there are three different things being discussed in that very title. One, human cells, human tissues, and three, products created from cells or tissues. And therein lies the potential ambiguity. There is a very big difference between the original form of a tissue and the original form of cells. The ambiguity is more pronounced when we consider the multiple cell types in something like adipose tissue.

In removal of adipose for adipose transfer, the tissue would be washed. This process is designed to remove blood, cellular debris, and liquid oils from disrupted cells. The very process of harvest will, of course, effect

changes to the tissue and cells. However, the vast majority of individual cells are affected minimally or not at all. Conversely, the tissue as a whole is changed more so. One coherent piece of adipose residing in an area of the body becomes a collection of adipose fragments having traveled through a three millimeter cannula.

To be able to move the adipose tissue and cells from one place to another for adipose transfer, one can break down the tissue with a scalpel, or one could break it down with a suction device. These mechanical procedures both yield adipose tissue as more useable at the donor site with the difference being largely in size and shape. The difference in size and shape being allowed under the same surgical procedure exception, what then is the difference using additional mechanical means to further the size and shape of small adipose particles into the stromal vascular fraction.

Unless this is addressed and clarified, it remains difficult from a legal and regulatory

standpoint even though the procedure is scientifically and medically well-founded and does not increase the risk of communicable disease any more than those typically associated with surgery. Thank you.

DR. WITTEN: Thank you. Next is the Long Island Plastic Surgical Group.

DR. DAVENPORT: Hi, my name is Tom Davenport. I'm a plastic surgeon at Long Island Plastic Surgical Group. I'm on staff at Stoneybrook University Medical School, but I'm not here representing that institution. I am here, however, representing patients who have benefited from dehydrated human amniotic chorionic membrane products.

I first also wish to apologize. A lot of the pictures I'm going to show are graphic, but I think it's important that there are patients who are really benefited and there are very few products which I have found to be as useful.

I come from a very, very large group of 23 plastic surgeons, and I get referrals from 23

other plastic surgeons, basically cases they don't want to take care of or they can't take care of. It's a very unusual practice. We have five wound care centers. We have 30 hospitals, and 23 surgeons.

I asked my PA to pick a slide which describes our practice, and he picked this slide. I'm a microsurgeon, so if you get your hand cut off, I put it back on. I also do procedures. This is a 12-hour procedure where I did a lateral thigh flap to reconstruct someone's ankle, and this is what it looks like. But not every patient can have a 12- hour procedure.

So my motivation is purely selfish reasons here. I look at the use of amniotic membrane as a big part of my practice. And in terms of healing patients, it's very, very important. The two patients I'm going to show here today actually wanted to come today, but I told them I would come and represent them for this purpose of this talk.

So this is my practice. It's entirely

getting out of Dodge in many situations. You have all these referring doctors, they send to me for a free flap.

My first patient, 84-year-old male, ankle wound. And by the way, we've treated over 150 patients with these or similar products. Patient has peripheral vascular disease, diabetes, pyoderma, renal transplant, renal failure, and he's been on steroids for 25 years. He has pyoderma. He also has this other wound -- this is not why I'm here -- and he has this ankle wound. The patient came to me because it was recommended he get an amputation. The patient is not even in a condition to get a haircut, let alone a 12-hour free flap.

This patient also was treated on his pyoderma wounds and the wound healed up. We did a skin graft and this patient was able to have a limb salvaged and not get an amputation. His pyoderma wounds also healed up as well.

This is another patient, 50-year-old patient with Wegener's. He had a neck wound for

two years, failed dressing, sent to me for a free flap. This patient came, had this neck wound. We tried skin grafting it and the skin graft at first took and then the wound kept getting larger and larger. As time went on, the skin graft melted away. We skin grafted again. It continued to melt away. He eventually had exposed carotid artery, was failure -- was having something called a carotid blowout, which is fatal if it does happen, especially in a 50-year-old.

I then called the institution that the patient was sent to us by. I'm not going to mention any names, but the initials are Johns Hopkins, not far from here.

We were able to salvage this patient by putting him on massive, massive doses of steroids and basically treating him like a bone marrow transplant patient. These are all just pictures of his carotid, and we were able to salvage.

He then went and wanted to get his ear reconstructed after we managed to salvage the patient. He went to another physician where he

had the free flap done, and he developed this wound where he would develop a pyelinital cyst. It was not a pyelinital cyst. It was a recurrence of his pyoderma in a worse area. So I tried dehydrated human amnion chorion matrix. It healed up in three treatments.

The patient then went back to the other institution, and when they did the second stage, his pyoderma came back in his neck. He was treated at the other institution for about nine months. After one treatment, the product called Epifix, it healed with one treatment. And this is a patient, again, nine months of steroids, Methotrexate, and several other autoimmune treatments.

So in closing, it's a very important product in my practice. And I know we're talking about all of these other different issues with regulatory issues, but I think it's important that we really keep the patients in mind and keep the importance that some of these products really have a huge impact on patients' lives. Thank you.

DR. WITTEN: Thank you very much. Our next speaker is from the National Spine and Pain Centers.

DR. FRIEDLIS: Hi, my name is Mayo Friedlis. I'm medical director at National Spine and Pain Centers. I'm here on behalf of my patients, though, not on behalf of that organization. I'm an interventional pain physician, and much of my practice today deals with regenerative treatments to deal with musculoskeletal problems that didn't have good solutions with what we had available. So it's on behalf of those patients that I am testifying today. Thank you for allowing us to testify and make statements to help you with your guidance.

As a practicing physician, the things that I think need to be discussed are bone marrow aspirate. It's quickly becoming a standard of care for many projects. Many treatments in orthopedics is bone marrow aspirate safe. And what does "homologous use" mean for bone marrow concentrate? That's where I want to focus my

discussion today.

The current use of -- well, let's go to this one. What can bone marrow concentrate offer for musculoskeletal pain, which is my area of concentration? First of all, it's an extremely low toxicity. There's been no recorded case of allergic or allergy rejection, no recorded case of other adverse tissue growth, no recorded case of cancers. High safety margin in a study of over 2,300 patients receiving same day bone marrow aspirate. The adverse event occurrence was.5 percent. That's compared to 6 percent on a total knee replacement.

So it's also safer than steroid use, surgical intervention or management with opioids. Much more cost- effective than other available options. More effective for many conditions, such as rotator cuff tears, ACL repairs, lateral epicondylitis, early osteoarthritis, and others. Additionally, it can slow the progress of the catabolic demise of joint degeneration. In our country we are seeing a younger and younger age

group getting osteoarthritis of the knees and hips in their 40s and 50s. These don't have good solutions because a replacement only lasts 15 to 18 years, which means they're going to have to have more than one in their lifetime.

Replacements offer a whole higher level of risk. There's reasonable proof of efficacy for these procedures. More, in fact, than in many orthopedic procedures currently done.

So what is homologous use for bone marrow concentrate? The assumption is that mesenchymal stem cells are somehow trapped in the bone marrow and maybe they go into the circulation and that they're somehow not involved in the healing of other tissues. There is evidence to show that they are in fact involved in the healing of cartilage repair, muscle repair, tendon repair, and bone repair.

We know this from, in the case of cartilage, from the procedures called microfracture, where the cartilage is in fact drilled into to get the bone marrow concentrate,

the stem cells if you will, up from the bone marrow to help heal the cartilage, which in fact they do to a degree with highland type cartilage. And we also know that the level of healing is dependent on the number of mesenchymal stem cells, that we can actually increase this healing by adding mesenchymal stem cells to the surface.

In muscles, which are usually healed by stem cells right next to them called "satellite cells," we know that when those are depleted, they'll just grab mesenchymal cells from the circulation which are right nearby and they will be healed with those.

Bone marrow concentrate -- or bone marrow mesenchymal stem cells, that is, are shown to be extremely important for tendon repair in rotator cuff at the ligament/tendon level, and also in bone.

In conclusion, let me just say that the use of bone marrow aspirate is important for the treatment of musculoskeletal problems. There is absolutely no evidence of any dangers in using

mesenchymal stem cells for treating painful conditions in the musculoskeletal system. There is no evidence of increased risk to the public using bone marrow aspirate for the treatment of orthopedic musculoskeletal injuries or degeneration. Bone marrow aspirate is in fact safer than other alternatives, such as steroids, surgery, and opioids. The treatment of cartilage, bone, ligament, muscle, all represent homologous use of bone marrow aspirate. The loss of these treatments will reduce the quality of care available to the public.

Thank you.

DR. WITTEN: Thank you. We're now going to take questions from our panel to the speakers. And then we will start on the next session, Session 3, of several of the speakers, but take a break before we ask questions of that set of speakers.

So I'd like to start. I have a question for Keith March, if he's still here.

Firs, I would like to thank all the

speakers for their presentations. I think it is helpful to hear everyone's perspective.

So, Dr. March, I'm not trying to put you on the spot like I did inadvertently with the other speaker this morning, but one thing that's always helpful for us when we write guidance documents is to have examples and examples of something that fits into a certain principle and examples of things where the principles -- it would not fit within what's described by the principles. So you proposed a concept of thinking about functional homology.

And Dr. Caplan, I want you to start thinking about this question, too, because I'm going to be asking you right after I finish with Dr. March.

I just would be interested to hear if you could just provide some examples of things that you thought demonstrated or fit within this concept of functional homology and some examples where you thought that that criteria was not met.

DR. MARCH: Okay, I'll --

DR. WITTEN: And your idea. I mean, your idea of this.

DR. MARCH: Yeah, I'll do my best. So an example of a functional homology would be if we take the mesenchymal stem cells from the adipose tissue, also known as adipose stem or stromal or secretory cells, and we put them with endothelial cells from any of a variety of sources in vitro or in vivo. Those two cell types can work together to form -- the two evolve to form a neovasculature and it's clearly a case of adult vasculogenesis going on. You can do that whether it's with adipose stem cells or with the mesenchymal stem cells from bone marrow or a host of other sources.

Conversely, you can take the adipose stem or stromal cells and do that with endothelium that comes from the skeletal muscle, that comes from the heart, coronary microvascular, or macrovascular endothelium that comes from the lung. And we've published and many others have also published these kinds of results.

So the point is that that would be one

example of where these cells are functioning to engage in and permit a two-cell based vasculogenesis. And it doesn't really matter which organ their partner cell, the endothelial cell, is coming from, it still does the same sort of thing. That's on the vascular network side.

Another example which has been emphasized by several is the paracrine property in the sense of perhaps parenchymal rescue. So not necessarily only considering the support of the vasculature, which Dr. Caplan elegantly pointed out, is that's the one side of the perivascular cell quite literally, the luminal side. But the abluminal side, the side that faces out from the blood vessel is useful in supporting and modulating both survival and in modulating the inflammatory response that's going on in the parenchymal side of the organ.

And so we have a number of assays for that. Again, both in vitro and in vivo. You can take the adipose stem or stromal cell and place it in a transwell membrane assay.

Let's take in vitro first and place it above or not far from but still in communication with through the media some other cell type. And this other cell type could be a myocardial cell. It could be a neural cell. It could be a pulmonary epithelial or endothelial cell. We've tried all of these and quite a few others in fact. And in each case you will find a very antiapoptotic effect in the context of stresses, whether inflammatory or reactive oxygen species mediated. And it doesn't matter which organ's parenchyma that you're looking at the cell effect of the ASC's as they secrete across this membrane. In every case you see a very parallel rescue and a turndown of the stress responses that ultimately can lead to apoptosis or necrotic death of the other cell.

Similarly, when we provide the ASC's in vivo in a variety of either ischemic or inflammatory situations, organ by organ, we see a similar response.

So those would be the two that I would

really call into mind. The functional homology that occurs when you're supporting the blood vessel, the vascular side. And the functional homology that occurs when you're modulating, usually down modulating, the inflammatory and the stress response on the parenchymal side of the organ. And those would be shared whether you're dealing with an ASC or an MSC. It just happens that it's easier to get ASC's. Sometimes I joke that I had too many of them so I had to figure out what to do with those guys. But everyone, even thin people, can use a little bit of their fatness, especially if we're talking an antilogous environment, as much of this discussion has been. It's much more difficult to get the MSC's from bone marrow. It's much, much more difficult to get it, in fact impractical, from other sources, brain, intestine, a lot of places they live, but you could do it. It's just that it's convenient to get them out of fat. And that's what I mean by the anatomy isn't really dictating the function, so that's why I urge that we think about a

functional homology.

Is that helpful?

DR. WITTEN: Yes, thank you. Wait, before you sit down, another question.

DR. ANATOL: So you had several recommendations during your talk, and I don't think you got to give your last recommendation, the regulatory consideration. I was just wondering if you could take a minute or two just to let us know what that was.

DR. MARCH: Sure. What I was thinking, I think this has actually been touched on by some of the other speakers, I think that in many instances our concern as a collective community is to ensure that the general principles of good clinical practice are being followed and that good facilities are the ones in which the products are being delivered. So as distinct from talking only about the product, as in one part of my discussion I urged us to consider more liberal consideration for some of the products. But I think that could be balanced by a more careful vision into the

facilities. And so just as there is the domain of HCT-type registration, I think that we could consider that in a good clinical practice paradigm with facilities that are doing these kinds of procedures. And that might be an appropriate balance whereby a facility is registered and perhaps the practitioners there are registered.

Now, in fact, I think that the FACT, the F-A-C-T, the Foundation for Accreditation of Cellular Therapy, as well as the ABB, have engaged in some of these kinds of things in the past. But I was wondering if perhaps stepping back and considering from the FDA perspective the notion that facilities and their practitioners may be able to be held to particular standards so we can obviate, for lack of a better term, the sort of strip mall concept but promote and promulgate the appropriate and the best sense human trials and experimentation in a registry format that occurs in the context of centers which are well known to be excellent in all their aspects.

I have some other things that have

little numbers on them, but I don't want to make myself say the wrong numbers of.10 and.15, so I will submit that in a subsequent comment. But it enlarges a bit on what I've just said.

DR. WITTEN: Okay, thank you. Dr. Caplan?

DR. CAPLAN: I'd just like to make one point, that there are published papers on MSC-like cells from a variety of sources from fat, from liver, from heart, from kidney, from marrow, where the transcriptomes of those cells in culture are -- been analyzed. And they have a number of transcripts in common and they have some unique transcripts for those tissues.

And so the fact that you can take fat-derived MSCs and you can take marrow-derived MSCs and put them in a variety of assays, including immunological assays, and get the same readout is interpreted by me and many of my colleagues to say that -- and what's missed, I have to say, by many experimentalists, is that the MSCs have huge sensory capabilities. They can

assay the microenvironment that they're in, but they have a hard-wired response profile.

And so, therefore, if you have stroke or you have heart attack and an MSC is given externally and goes to those two different sites, they will do the same sorts of things, but they will use different molecules and different molecular mechanisms. And we're only now starting to understand some of those mechanisms.

In one study at Case Western Reserve University, it's very clear that the injured tissue sitting next to an MSC compared to the normal injured tissues making 90 different transcripts. So the therapeutic proteins in all likelihood are coming from the host, not from the donor. And this is I think an important point, which is these cells in vivo, when they're put back or they're energized in vivo, they actually are sentinels for injury and assist the host in regenerating tissues.

That's why I have strongly argued for clinically homologous use. My knee joints, my

elbow joints, and my shoulder joints are all killing me at the moment because of my age and because I didn't choose my father properly. And in this case the MSCs can have a very strong medicinal effect. One of the clear medicinal activities of MSCs is they make molecules whose names we know that sit on opioid receptors. So the perception of pain is decreased without taking opioids.

And so this is another clinical aspect. How can we call -- how can we justify homologous use of taking fat- derived MSCs and only using them in fat when -- or having fat tissue that has dispersed MSCs in it as a therapeutic modality?

So again, I strongly oppose the concept that concentrated bone marrow is an MSC product because there's probably five MSCs in concentrated marrow. But there's a strong, very strong, paracrine activity of concentrated marrow, the details of which nobody knows. But it has some reported clinical outcomes.

And so although a hundred years ago we

ground up dog pancreases and gave it to diabetic patients with fabulous clinical results, it's only taken us a hundred years now to fabricate insulin, human insulin, and deliver it to diabetic patients. The cell-based therapies that are being proposed and being tested clinically by investigator- initiated clinical trials are curative. That's not what you can say about any insulin product currently on the market. And I think that's an important aspect. And the aspect of curative is gigantically innovative.

And one last sentence is that the unexpected activity that MSCs make antibiotic proteins, LL37, that kill bacteria on contact is currently being tested with an appropriate FDA-approved IND in cystic fibrosis kids who have horrible lung infections. This can actually be curative for those lung infections if we can get this unusual antibiotic protein physiologically directed at the invading bacteria. This, I think, is an important completely non-homologous use of these cells. However, from a paracrine standpoint

totally homologous.

DR. WITTEN: Thank you for that and for that example. I think it's time to see whether there are questions from the panel for some of the other speakers. Thank you, Dr. Caplan.

Other questions?

DR. ANATOL: I have a question. So this question is for the speaker from Wake Forest, which I think might be Dr. Allickson. So in your presentation you provided some examples that we should consider as we move to finalize the guidances. And for the homologous use guidance you suggested we include an example that when amniotic membrane is placed over wounds to retain moisture this should be considered homologous use. I'm just wondering if you see this use as different than a wound covering function of amniotic membrane or whether you would consider them the same?

DR. ALLICKSON: No. What I was suggesting would be simply a barrier for wound healing. So I thought that that fits within the

361 if you look at all of it. And I thought that it's an example that hasn't been demonstrated. I thought it would provide clarity for people that are working in that area.

DR. ANATOL: So as a barrier specifically for wound healing?

DR. ALLICKSON: Yes.

DR. ANATOL: Okay. Thank you.

DR. ALLICKSON: I will submit those comments. Thank you.

DR. WITTEN: Okay, any other questions from my colleagues on the panel?

We're going to move on now to Session 3. And we'll start -- our first speaker represents the Academy of Regenerative Practices.

DR. COMELLA: Hi, I'm Kristin Comella and I'm the president of the Academy of Regenerative Practices. The Academy of Regenerative Practices provides information and educational programs on the clinical uses of regenerative and stem cell therapies. The ARP promotes regenerative medicine by teaching

physicians integrative and comprehensive treatment methods, including bone marrow and adipose stem cells and platelet rich plasma. And the ARP is dedicated to providing physicians with the latest regenerative clinical practices and providing the data to support these therapies.

The role of physicians is to dedicate their lives to serving the interests of the patient. Market forces, societal pressures, and administrative demands must not compromise this principle. The role of the FDA is responsible for protecting the public health by assuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, our nation's food supply, cosmetics, and products that emit radiation. The FDA does not regulate the practice of medicine. The FDA does not regulate our bodies and tissues.

According to the FDA's current laws, the implantation of autologous HCTP's during the same surgical procedure is the practice of medicine. And I think that this was discussed in the last

session very eloquently, the concept of homologous use and that the main purpose of cells is to repair and maintain the tissues. So this is in fact homologous use. In addition, many surgical procedures are using tissues in a non-homologous manner. And what we're dealing with in these in-clinic stem cell procedures are surgical procedures. So this is not a necessarily stem cell procedure. And these therapies, such as CABG with vein graft and ilium to replace the bladder are in fact using tissues in a non-homologous way.

Also, the concept of minimal manipulation was addressed earlier today, and this is a process that does not alter the relevant biological characteristics of cells and tissues. However, many surgical procedures currently used by physicians do alter the characteristics of tissues. So the concept of minimal manipulation does not apply to physicians in the surgical procedures that may be utilized such as skin grafts, hair transplants, bone grafts, and others.

The regenerative procedures performed in

clinic using the patient's own tissue do not constitute a drug and, therefore, should not be regulated by the FDA. Medical professionals have jurisdiction over surgeries and procedures on patients. Patients have a right to provide informed consent on procedures involving their own body and tissues.

I wanted to give a few examples of cases that we've seen in our clinic, as well as other physicians have provided me some of their slides to use.

This is an example of a patient with very thin skin, vasculitis, and as a result gets these non-healing ulcer wounds repetitively. And nothing was successful for this patient. When all other medical therapies have failed, this is an example where cell therapy using SBF and platelet rich plasma was successful in healing wounds.

We also see very good results in orthopedics. This is an example of a patient with osteochondritis, and you can see the bone lesion prior and then post full resolution.

We also have good results in osteoarthritis, patients who are bone in bone with limited joint space showing increased joint space after an injection that was done in clinic by a physician using stromovascular fraction and platelet rich plasma.

We've done a handful of studies and attempted to publish many of these studies and have been successful in publishing these. Unfortunately, there is a lack of funding available to do these studies. So we're counting on using the funds from our own, oftentimes foregoing salary to perform some of these trials for patients. And we've been successful in studies with degenerative disc disease as well as COPD. And this is an example of patients who demonstrated statistically significant improvement in flexion.

This is an example of a patient who had a cancer and as a result had radiation done from the nose down to the chest. And as a result, the glands had been completely destroyed, so he was no

longer able to produce saliva. And what he told us is that he was actually suicidal because he was no longer able to talk, to sleep, or to eat food because of the lack of saliva in his mouth. After injecting the stromovascular fraction cells directly into the glands, he now is producing saliva and is able to live a normal life eating food. Why would we deny this type of therapy to this patient?

We've done a handful of patients for traumatic brain injury. Many patients who are wheelchair bound and unable to talk or walk are now coming out of their wheelchairs and telling us full sentences about the day that they were injured. These were chronic patients two-plus years post accident and now performing normal activities that they never dreamed and that their family never dreamed that they would perform.

I want to share with you two cases. This is a patient with MS who was wheelchair bound and her physical therapist is wiping away tears as she is now walking on a walker. And her husband

called me to tell me he was so excited because she did laundry for the first time in five years. I'm not sure that's the first thing I would do.

This is a spinal cord injury patient who was wheelchair bound two years post accident and his mother said that every day he asks her to kill him. She stands in the kitchen wondering if she's going to have to kill her own son and would she kill herself next? And now he is able to walk with assistance and move his legs. He had no movement from his chest down and limited use of his hands.

These are life-changing techniques. When we move these therapies forward, there are going to be setbacks. There are going to be some adverse events. But that can't stop the field from moving forward. We have an obligation to our patients and to the community to rapidly move these therapies forward.

I want to share with you two examples. In 1928, Alexander Fleming discovered antibiotics. And at the time, his colleagues laughed at him.

He actually was giving away his antibiotics, penicillin, for anyone to test in the lab because he felt that it was something that was very important. It wasn't until 12 years later and he had actually abandoned the idea of penicillin being something important that would change medicine. Twelve years later there was a paper published by Oxford, and at that time it became very apparent that antibiotics were going to change medicine. I think we have something very similar on our hands right now.

The other example I want to share with you is bone marrow transplantation. From the years 1939 to 1969, there were 203 documented cases. If we applied the same rules that we have in place or that we're trying to put in place now, this therapy would not have progressed forward because 152 of the first 203 patients died.

These therapies are going to change medicine just as bone marrow transplantation has changed medicine. And it is important to note that the first double-blind, placebo- controlled

trial for bone marrow transplantation was not done until 1998, years after this had become the standard of care.

We are the Academy of Regenerative Practices and it's time to bring these therapies forward to patients. Thank you.

DR. WITTEN: Thank you. The next speaker is from the Alliance for Regenerative Medicine.

DR. WERNER: Good afternoon, my name is Michael Werner. I am the executive director of the Alliance for Regenerative Medicine, also known as ARM, A-R-M. We are the preeminent global advocate for regenerative and advanced therapies, fostering research, development, investment, and commercialization of transformational treatments and cures for patients worldwide. ARM is comprised of about 240 life sciences companies, academic research institutions, clinical centers, patient advocacy groups, and investors who have come together to support research and product development in cell therapy, gene therapy, tissue

engineering, and other advanced technology sectors.

Thank you very much for letting me speak today to provide our organization's views about FDA's draft guidances related to human cells, tissues, and cellular and tissue- based products. ARM welcomes the publication of the draft guidances and commends the FDA for holding this public meeting. Of course, how FDA interprets the relevant provisions of the Food, Drug, and Cosmetic Act and applies its regulations is critically important to ensuring that safe and effective products and therapies reach patients as soon as possible. And we know that's a goal FDA shares and indeed it's a goal I think everyone in this room shares.

We've provided written comments in the docket regarding the draft guidances, which have a lot of very specific points in there and specific examples of minimal manipulation and homologous use and all of that. So what I'm just going to do is summarize our views.

And generally speaking, it's important to know that ARM has a diverse membership. And our members develop products and do research on products that really range the spectrum regulated by FDA under these guidances. So, for example, we represent manufacturers of products regulated under Section 351 of the Public Health Services Act that requires an FDA marketing authorization. We also represent companies with products that are regulated only under Section 361 of the Public Health Services Act and do not require a marketing authorization from FDA. But what all manufacturers have in common, and really what we've heard from many, many speakers here today, is that we need to have a clear and predictable regulatory pathway to market with easy to understand rules uniformly enforced. And in general, ARM believes that while the draft guidances are a good step forward, they still leave some questions unanswered regarding interpretation of regulations.

Consequently, ARM believes that when FDA

finalizes these guidances, it needs to take actions to provide more clarity. This could take several forms. Further clarification on requirements for product characterization and related claims for each type of product would be helpful. For instance, we urge FDA to publish even more examples of how the key terms such as "minimal manipulation" and "homologous use" will be applied to various technologies. This would include when certain technologies, such as adipose tissue, as we've heard a lot about today, would or would not be considered more than minimally manipulated and where so-called repair, reconstruction, and supplementation lead to findings of homologous use or not. Along with these examples, we want -- we urge FDA to provide detailed rationale to provide even more clarity about its thinking.

In addition, ARM urges FDA to provide flowcharts in the guidance to clearly demonstrate the agency's thinking regarding evaluation of these products. This would give researchers and

product developers a step-by-step process to determine how their product will be regulated. The agency could supplement its regulations and guidance and include these flowcharts actually in the guidance, and that would help everyone understand and navigate their way through the guidance and also provide the agency's assessment criteria in a logical sequence. And we actually provide examples of those in our written comments.

Finally, we think that FDA should look for ways to communicate a more detailed summary of the rationale for its regulatory decisions. So for example, the Tissue Reference Group, the TRG, processes and decisions can be made more transparent. ARM urges FDA to add an appendix to the draft guidance that details TRG decision-making processes. It would also be useful to reference where the TRG recommendations are published. In general, ARM would encourage FDA to allow increased interactions with sponsors during the TRG process, and the agency should publish a more detailed summary on the rationale

for each TRG classification recommendation. Moreover, the website, the TRG website, should be updated within one quarter of activity.

So I want to now turn to just a summary of some specific comments on the minimal manipulation and homologous use draft guidance. So in terms of minimal manipulation, our comments are going to address specific terminology and provisions, such as we are concerned about the guidances' use of the term "main function," not currently a term used in regulations. If FDA is going to use the term "main function," it needs to be properly defined and not just in a "such as" manner as it is now.

ARM would like to see the agency confirm that the previously released list of processing steps in the preamble to the 21 CFR 1271 regulation, which was published in 2001, remains the current agency thinking. If the agency thinking has changed, we request that the draft guidance identify under what circumstances, if any, the criteria outlined in 2001 would not

constitute minimal manipulation.

Centrifugation should be specifically called out as minimal manipulation except where it may affect relevant characteristics of the tissue being centrifuged. This would bring FDA's guidance in line with European Advanced Therapy Medicinal Products Guidance, which is followed by most regulatory authorities.

ARM believes the guidance should clarify with more examples at what level a tissue structure must be preserved to be considered minimally manipulated. The guidance implies but does not explicitly state that the primary structure, including the load-bearing properties of the tissue, may be changed so long as the underlying tissue structure is unaffected.

In terms of homologous use, the guidance contains a lot of precise terminology, and we would recommend a glossary with definitions of key terms to be used in the guidance as a way to provide further clarity on how the terms should be interpreted and understood. Alternatively, FDA

could add a reference in the guidance to the definitions provided in 1271.3, which ensures that these definitions reflect the agency's current thinking.

FDA should provide additional clarity on its decision to distinguish between structural and nonstructural tissue and cells in its definition of homologous use. We're concerned that the definition provided in the document does not consider the same basic function in a way consistent with the guidance preamble. We recommend the list of basic functions of amniotic membrane be expanded to include covering and protecting. And we recommend the FDA add another subsection to define in more detail how homologous use applies to HCTPs intended for wound healing, including examples.

ARM appreciates FDA's efforts to continually improve, clarify, and update its guidance in this area, and we remain ready to work with the agency on the issues in the days ahead. Thank you.

DR. WITTEN: Thank you. Our next presentation will be from the Alliance for Advancement of Cellular Therapies.

DR. MILLER: Doctor Witten, members of the panel, ladies and gentlemen, my name is Leslie Miller, and I am the chairman of the Executive Committee of the Alliance for the Advancement of Cell Therapy, which is an organization composed of patients, clinicians, and scientists involved in not only the advancement of the field, but the very responsible use of cell therapy.

I speak today as a practicing cardiologist and a clinical trialist with experience in over 100 clinical trials, following FDA protocols and currently enrolling for trials. So I have a fair perspective on this problem.

There is clearly a very significant interest in this topic as evidenced by the attendance in this meeting and the petitions to speak. And I think this reflects the interest in what is addressing one of the most important healthcare problems in the U.S. and around the

world, and that is chronic disease. These therapies offer potential therapy in a myriad of conditions. More money is spent for the care of people with chronic diseases than any other item in both federal and private healthcare policies. And that has to account for the greatest cause of disability and loss of productivity. There are estimates that range in the tens of millions of people afflicted with chronic diseases, and with the advancing age of this population, this is going to become a more pressing problem with each passing year. This cost is not sustainable and new solutions need to be found.

We acknowledge that the FDA is facing a very significant challenge in how to optimize the many rapid advances taking place in many diverse uses of cell therapy occurring in this field while maintaining the health and safety of products. We share this commitment to safety and high standards for cell therapy. But research has become slow and almost prohibitively expensive under the current guidelines. They lead to clinical trials

that have often been underpowered to answer critical questions on efficacy, which delays progress in the field. We believe that the very pressing health problem of chronic disease warrants new approaches to regulation.

One new approach is embodied in the Regrow Act, which is about to be considered by Congress. This bill is not intended to alter FDA's oversight role over cell therapy but provide enhanced flexibility and much quicker access for patients to those cells and strategies that are shown to be both safe and reasonably effective in well-controlled and randomized phase 2 trials with increased numbers of subjects to really test the therapy being evaluated and avoid the extremely high cost of phase 3 trials.

There is ample precedent internationally for adoption of accelerated pathways and conditional approval for cell therapy in countries like Japan and China, many countries in Europe, as well as most recently Canada. We are now behind these comparable countries in our response to this

important healthcare problem. Acceleration of the approval process is feasible based on the substantial record of a high degree of safety, particularly autologous cell therapy, with many med analyses showing as little as 2 to 4 percent incidence of significant safety problems.

The problem in this field is that the use of cell therapy has evolved rapidly from being available only in FDA-approved clinical trials to essentially an unregulated use in well over 500 clinics in this country, as well as a large number outside the U.S. by practitioners with highly variable training and competence. This has led to many valid criticisms of this unregulated use, but painted with a fairly broad brush, and has led the FDA to seek an all- inclusive set of guidelines, which would essentially shut down clinical access to this therapy in the United States. This would not only drive thousands of patients to clinics outside the United States, but also disadvantage the poor and those of limited resources and markedly diminish the chance to gain important

clinical experience and trial experience with cell therapy to prove its safety and efficacy.

We believe that there's a reasonable alternative to total suppression, and that is the creation of a registry of cell therapy. There is ample precedent of using a well- curated registry even as a control group for many phase 2 and phase 3 trials, including mechanical assist devices, as well as their value in providing very important non-protocol real world experience with a treatment importantly that may show outcomes that may differ from clinical trial data, both better and worse. We believe that a registry could address most of the valid criticisms and concerns about the current unrestricted use of cell therapy.

In order to participate, a clinic would have to meet very rigorous criteria. To address the concerns about incomplete data, the clinic would agree to enroll every patient treated for every indication and provide de- identified data on the indications, symptoms, and demographics.

To address the variable quality of cells delivered, they must obtain certification of their cell preparation lab or the vendor they're using and provide complete data on source preparation type, number, quality, route, et cetera, of the cells delivered. To assure the valid treatment strategies, they would use IRB approved protocols for every indication based on published data.

To address the major concern that patients get variable and potentially inflated expectations of this therapy, we propose the use of a novel scripted narrative that can be reviewed and approved by the FDA, which would then be videotaped and provided to each patient to assure a fair and balanced information provided to their families as well to allow adequate time for questioning before they commit and consent to these procedures. And it would include consent to provide required follow up.

To address the lack of reliable meaningful data there'll be the use of only endpoints and metrics utilized in published

clinical trials. The mandated follow-up would occur with trained objective observers to document both good and adverse outcomes. To assure the reliability of the data without internal conflict, they would use an independent company to control all data and assure compliance. The patients and the clinics would submit all data within one month of the uniform time or be potentially suspended for a period until that data is up to speed.

One of the most important aspects of the data in the registry is complete transparency and the ability to audit every aspect of the data, including outcomes, by the FDA. But also for patients who are seeking treatment to assure the highest quality centers and treatments with real time available to make the most informed decision.

We have no doubt that this recommendation would reduce the number of clinics providing cell therapy to a relatively small number initially. But we believe that this could provide the FDA with a much needed high quality data on safety and efficacy of cell therapy and

allow continued access for patients of those clinics that are willing to meet these very high standards with enhanced confidence of very high quality care.

I hope the FDA will consider this proposal. Thank you.

DR. WITTEN: Thank you. Our last speaker before the break is from the Alliance of Wound Care Stakeholders.

DR. KIM: My name is Paul Kim. I'm pleased to be here today representing the Alliance of Wound Care Stakeholders. The Alliance is a nonprofit multidisciplinary trade association of physician medical specialties, societies, and clinical associations whose mission is to promote quality care and access to products and services for people with wounds through effective advocacy and educational outreach in the regulatory legislative and public arenas. Several of the professional organizations to which I belong are members of the Alliance. Most of the Alliance clinical members use tissue products in their

practices and thus have a vested interest in ensuring patient access to these important products, which may be jeopardized based on the language contained in the guidance documents.

By the way of background, I've been working in wound care and limb salvage for the past 11 years. I'm an associate professor in the Department of Plastic Surgery and the director of research through the Division of Wound Healing and Hyperbaric Medicine at Georgetown University Hospital. While I'm speaking on behalf of the Alliance, many of my comments are based on my own personal clinical experiences both in research as well as in treating patients with wounds with the types of products that are the subject of this hearing.

My comments today will focus on two of the four guidance documents, minimal manipulation and homologous use. These two concepts are so interrelated that while it is appropriate to have separate guidance documents for each, there must be consistency between the two documents.

Furthermore, while each of the guidance documents should provide specific detail or to give greater clarity and guidance, this does not occur in these particular documents. In fact, many examples that were previously provided have been eliminated. More importantly, there are too many significant new requirements within the minimal manipulation document which not only conflict with homologous use document but conflict with the current regulatory language.

There are two main areas of concern for the Alliance in the minimal manipulation document. Number one, the term "main function" introduced in this document conflicts with the current definition of "homologous use." Number two, the change regarding how minimal manipulation is determined that specifically focus on the main function of the tissue in the donor rather than what is written in current law by the function of the tissue in the recipient.

First I'd like to address the newly created term "main function" in the minimal

manipulation guidance document. The notion that these tissues have a main function which determines whether a product is structural or nonstructural conflicts with the current regulation, as well as the draft guidance document on homologous use. The conflict with homologous use guidance is problematic. It is not possible to separate homologous use from minimal manipulation. When considering whether or not a product is regulated as a 361 ACTP, the homologous use guidance document accurately utilizes the term "basic function/functions." And we recommend that the FDA continue to utilize the term "basic function and/or functions."

Furthermore, it is misguiding and clinically inaccurate to state that the tissue has a main function. Tissue products have more than one function, and to restrict their use to one function, the main function, is scientifically and clinically incorrect. Tissues even without cells may have more structural impact upon application or implantation.

For example, amnion contains not only collagen in an extracellular matrix, it has other proteins and other biologic that provide other biologic functions. Minimal manipulation of ECM and processing should maintain the ECM biochemical factors such as fibronectin, gags, PGs, and laminates that are local biological effects like the organization of cell migration and facilitation and cell attachment that are beyond providing a simple structural support. Cell attachment elicits another cascade of activity related to restoration of healing processes that were absent prior to placement of the donated ECM. We can't achieve this with synthetic dressings.

Many HCTPs have more than one function which should be included in these guidance documents. For example, there are different tissue types that we should be -- would be subject to this guidance, and all should be broken into specific areas, including but not limited to dermis, epidermis, amniotic, chorion. Each of these tissue types have multiple functions and not

simply a main function. For example, basic functions of placental tissue or amniotic membranes can include preventing infection, rapid self-restoration, allowing free movement, a protective barrier, and a cover. With or without maintenance of the donor cells, many of these basic functions are sustained and observed after placement in the recipient. By utilizing most of the basic function or functions within the definition of placental tissue, a clinician can apply placenta-derived tissues as part of good wound care, treatment for a variety of wound types and severity.

If the notion of main function was adopted, then dermis-derived allographs would not be used to treat wound care patients. Yet there are several studies published providing evidence of the clinical benefit of the dermis- only allographs when used in treatment regimen of full thickness chronic wounds.

The Alliance urges the FDA to eliminate the term "main function" and instead utilize the

term "basic function or functions of tissue."

With respect to the second issue, the FDA changes how minimal manipulation is determined. Under current law, whether an HCTP is considered to be more than minimally manipulated is determined by the tissue's function in the recipient. Thus, for structural tissue, the analysis -- excuse me, the Alliance is concerned with the effects that processing has on the tissue's utility for reconstruction, repair or replacement. The draft guidance, however, analyzes minimal manipulation, reports minimal manipulation in terms of main function of the HCTP. It focuses on the main function of the HCTP in the donor.

We are extremely concerned about this departure. Tissue adapts to its environment. Tissue is often explanted from one area and successfully used in different areas of the body. Just because a tissue may come from a uterus does not mean it must be transplanted into a uterus. Any tissue used must function in the recipient in

the manner required by that of the recipient, regardless of the product origin or the source of the material. The extracellular matrix of tissues are basically the same regardless of where it is placed. The microenvironment into which donated tissue is placed guides its remodeling, its functionality.

Historically, several sources of tissue have been used in wound care with success: peritoneum, fascia, pericardia, skin, placental membranes, and blood components. The Alliance recommends that the analysis should be based on the effects of the -- that the processing has in the tissue's utility for reconstruction, repair, or replacement in the recipient. It's not only more accurate, it is also what is currently required in the regulations.

The Alliance does have two specific issues regarding the homologous use guidance document. First, the Alliance is concerned about how narrow the definition of homologous use for amnion tissue will impact its use for wound care.

There are many functions of amniotic tissue, as we described earlier. And this tissue type should be used for wound healing. The FDA has even stated in the past that amnion may be used for wound healing when cytokines were present. Meaning that it was not decellularized. As such, the Alliance recommends that the FDA continue to permit amnion in their homologous use consideration.

Finally, the Alliance would like to state that regulations expressly do not separate the definition "homologous use" depending on whether tissue is structural or nonstructural. And that's been raised before in this session.

On behalf of the Alliance, I thank you for the opportunity to provide you with our testimony. We'll be submitting written comments later this month.

DR. WITTEN: Thank you. We're going to take a break now. We're running a little bit early so that we'll reconvene at 3:15. So can everyone be back in their seats at 3:15.

(Recess)

DR. WITTEN: Our first speaker during this session will be from the American Association of Blood Banks.

DR. KAMANI: Good afternoon. My name is Naynest Kamani. I'm the vice president for cellular therapies and research at AABB, formerly known as the American Association of Blood Banks. AABB is an international not-for-profit professional association representing approximately 7,500 individuals and about 1,500 institutions involved in the fields of transfusion medicine and cellular therapies. AABB advances the practice and standards of transfusion medicine and cellular therapies to optimize patient and donor care and safety. AABB appreciates the opportunity to provide comments on the draft guidance documents relating to the regulation of human cells, tissues, and/or cellular or tissue-based products. Additionally, AABB applauds the FDA for its efforts to thoughtfully regulate the HCTP industry in order to maintain patient access to safe and effective cellular

therapies.

We have comments pertaining to three out of the four draft guidance documents that are the subject of today's public hearing. First one is on the minimal manipulation of human cells, tissues, and cellular and tissue-based products. AABB requests clarification on two sections of this document. First one, the working definition of "minimal manipulation" and the second on the specific examples of nonstructural and structural tissue.

With respect to minimal manipulation, we request further clarification on whether forms of processing such as cutting, grinding, or enzymatic digestion of tissues such as cord tissues prior to cryopreservation for potential future isolation of cells such as mesenchymal stromal cells would meet the definition of minimal manipulation.

Secondly, in the same guidance document, the FDA has provided a limited list of examples that the agency considers as either structural tissues or as cells or nonstructural tissues.

AABB requests that these lists be expanded to include other tissues that are currently collected from donors and either stored or manipulated for subsequent use. We request clarification on whether tissues such as cord tissue are considered as structural tissues. Included on the list of examples for cells or nonstructural tissues are lymph nodes and parathyroid glands. We request further clarification on what other tissues, for example, tissues such as thymic tissue or the thymus gland, whether they would qualify as nonstructural tissues as well.

Our second set of comments is on the same surgical procedure exemption under 21 CFR 1271, questions and answers regarding the scope of the exception homologous use of HCTPs. AABB requests clarification on the requirements for intraestablishment transfer of HCTPs. The guidance states that the same surgical procedure exception applies when HCTPs are for autologous use implanted in the same surgical procedure and remain in their original form with maintenance of

safety and sterility. Temporary storage for a few days between the time of collection and use would qualify for SSP exception, as long as the HCTP is not manipulated other than rinsing, cleansing, sizing, and labeling, and the administration and collection are occurring at the same establishment. We need clarification as to whether the SSP exception is applicable if the stored HCTPs are being transported from one building or facility to another building or facility within the same establishment.

Our third set of comments is on the guidance regarding homologous use of HCTPs. AABB requests further clarification from the agency on the guidance for the homologous use of HCTPs for the following circumstances. First, we request the inclusion of examples in this guidance that address the use of whole blood marrow aspirates or enriched concentrates of bone marrow-derived stem cells or blood or bone marrow-derived platelet rich plasma, or PRP. We also request clarification on whether the effects of

platelet-derived growth factors in PRP are considered as having systemic effects. Because this would then have implications for whether it would be characterized as homologous use or minimal manipulation.

We appreciate this opportunity to provide these comments and will be submitting these in an electronic format within the next couple of weeks. Thank you.

DR. WITTEN: Thank you. Our next speaker represents the American Association of Tissue Banks.

DR. WILTON: Thank you. My name is Frank Wilton, and I'm the president and chief executive officer of the American Association of Tissue Banks, or AATB. In my allotted time, I would like to provide a brief background on human tissue and its safety, highlight some positive aspects of the guidance documents, and then summarize our key recommendations for improvement.

Before I delve into the specifics of the guidance documents, I want to first touch upon the

issue of safety. Like FDA, the AATB diligently monitors and audits tissue safety. If a safety issue is identified, the AATB quickly establishes new standards to further reduce the risk of potential harm. Due to that strong diligence, human cells, tissues, and cellular-based tissue products, or HCTPs, have a stellar safety record as outlined on this slide. Given that excellent safety record, I must admit that we at the AATB were a bit taken back by some of the FDA's current thinking with respect to the regulation of HCTPs as it is described in the guidance documents. We have worked to diligently respond to the request for comment and provide additional science background information related to the application to particular HCTPs and of course recommendations.

As we seek to improve the guidance documents, we must stay grounded in the supporting science and regulations. This slide contains two key aspects of the regulations. The first denotes the agency's presumption related to the application of the term "homologous use" and the

second highlights the opposing but supportive goals of maintaining safety and access or availability. So I will discuss in a few minutes our recommendations for improvements focused primarily on ensuring that the guidance documents more closely adhere to these underlying regulatory tenets.

Harkening back to the balance between access and safety, I provide this slide to simply highlight that, per our review of the guidance documents and further detailed in our comments, our primary concern is that more than a quarter of a million patients will be potentially denied access to currently marketed HCTPs. Given the safety record, it is unclear why the agency feels as if the access to current therapies should be dramatically affected.

As you probably ascertained from our previous comment letters, one key issue is the newly introduced concept of "main function." Procedurally, this is such a departure from current regulation that we feel it is not

appropriate for a guidance document but better suited for notice, comment, and rulemaking. The procedural shortcomings become even more important in light of our serious substantive concerns with this new term. Rather than focus on a predetermined function for a tissue category, such as all adipose, we believe the agency should retain its current review of HCTPs on a case-by-case basis. In that manner, it is the basic function or functions highlighted by the manufacturer's objective intent which determines whether a specific product is structural and/or nonstructural in applying the definition of minimal manipulation.

Under the previous regulations, the agency provided a list of processing steps that were generally determined to be within the rubric of minimal manipulation. However, in crafting these guidance documents, the FDA has omitted that list. We believe it should be restated and expanded. We understand the limitations of that list, that it applies generally and not

specifically. However, especially in light of numerous new guidance documents, providing some general clarity would be exceptionally helpful.

Before I delve into my next recommendation, I'd like to highlight how the agency described the process for determining whether a product was minimally manipulated within the 2006 Jurisdictional Update, or JU. As this slide highlights, the determination was made on a case-by-case basis, weighing the potential effects, both positive and negative. Unfortunately, the agency has moved away from that construct in these draft guidance documents and seems to be putting the onus on tissue banks and others to prove that a product is a 361 HCTP rather than weighing it on a case-by-case basis. We respectfully recommend that the agency revert to its previous position related to minimal manipulation and the eligibility presumption.

While I do have some comments on the homologous use guidance as denoted on this slide, I want to note that AATB was generally less

concerned with the latter developed draft guidance documents because, other than what is noted here, the homologous use draft guidance document primarily hues closely to the regulations and FDA's previous interpretations. And, most significantly, this draft guidance did not contain the new and poorly defined term "main function."

That said, I want to end my time in front of you on a positive note. Not only has the FDA provided a formal comment period, which did not occur with the 2006 Jurisdictional Update, but you've opted to have this hearing. In addition, recognizing that all these draft guidance documents are interrelated, you extended the formal comment period. Finally, we are pleased to note that you reflected upon our comments from the 2006 JU and included our suggested definitions of the terms "original" and "relevant." I'm hopeful that upon reading the final guidance documents the AATB will be able to note more situations where we feel as if our recommendations were truly heard and acted upon.

Finally, I would like to highlight that AATB understands just how difficult it is to develop key guidance documents. As the FDA is aware, the AATB shared its particular guidance document recommendation related to homologous use with FDA just before the FDA released its own document.

Further, since that time, the AATB, and in particular the Tissue Policy Group, or TPG, has focused on a much more comprehensive guidance document. This guidance document, which we will submit to the docket prior to the close of the comment period, expands upon the homologous use draft guidance document recommendation by adding new discrete concepts. Namely, as the title suggests, the main features of this guidance document recommendation is to provide a framework for the appropriate analysis, characterization, and assessment of HCTPs based on the manufacturer's objective intent. This document further details key linkages between core regulatory concepts growing on clear regulatory

link between the manufacturer's objective intent, the homologous use, the original relevant characteristics, and the appropriate methodologies for analysis, characterization, and assessment. Finally, it also contains HCTP flow diagrams, given the need for additional clarity in this area. The vast majority of tissue utilized within the United States follows this guidance already.

Thus, we hope the FDA will review this document in its entirety before finalizing the guidance documents. If we were not so pressed for time, I would spend much more time talking about this document given its importance. We encourage the FDA to hold a workshop on the topic and we would be happy to collaborate with FDA on it. Thank you for your time.

DR. WITTEN: Thank you. Our next speaker represents the American College of Surgeons.

DR. GLASBERG: Good afternoon. As a governor with the American College of Surgeons, I'd like to thank the FDA for convening this Part

15 hearing. My name is Dr. Scott Glasberg, and I'm pleased to be able to present to you this afternoon regarding fat grafting and its application crossover in a variety of surgical specialties.

First, I'd like to take the opportunity to provide you with some background on the American College of Surgeons. Founded in 1913, the American College of Surgeons was the premier scientific and educational organization for surgeons numbering more than 80,000. The American College of Surgeons is a global organization with more than 6,600 fellows in other countries, making it the largest organization of surgeons in the world.

As this slide highlights, the fat grafting procedure has three major components. Fat harvesting, in which the patient is anesthetized and the fat is usually removed by a stent or liposuction technique. Once harvesting, minimal processing is used to clean the fat and separate it from the lipoaspirate using methods

such as centrifugation, washing, and filtering. Then the fat is transferred and implanted into the desired location. To put it in simpler terms, fat grafting involves harvesting with liposuction or tumescence, simple processing, which may include centrifugation, washing, and filtering, and implantation of the graft with a syringe and blunt cannula. Most importantly this slide highlights activities that are not considered related to fat grafting by the American College of Surgeons and the American Society of Plastic Surgeons, namely concentrating stem cells, advertising related to the stem cells, or the addition of any types of additives, such as P188.

It is our understanding the agency is looking to produce a document that will allow surgeons to reflect and determine what is the standard and appropriate use of adipose cellular transplantation. So it's for this reason we've included these procedures which we felt fall outside the realm of current standards of fat grafting.

While most of you are familiar with fat grafting within plastic surgery, I want to highlight that fat grafting is used in many surgical specialties to help a variety of procedures, such as the reversal and modulation of scarring, modulating pain, including pain related to amputation sites, reversal of damage done by therapeutic radiation, the treatment of bed sores, medical care for vocal cord paralysis, therapy for velopharyngeal insufficiency, medical care for scleroderma and other systemic sclerosis, treatment for Dupuytren's Contracture and Reynaud's phenomenon, and additionally into joints in orthopedic surgery.

Of course, given that there's a wide application for numerous surgical related issues, it's important to ensure that within the practice of medicine there is appropriate informed consent. This slide highlights some of the key components of that consent process, especially as it relates to the long-term effects of fat grafting as well as combining it with other procedures. And

appropriate consultation involves a description not only of the procedure but the associated risk and safety issues for that procedure as well. Fat grafting is considered safe to be performed with other surgical procedures such as breast augmentation, revisional breast surgery, and breast reconstruction. There are many other surgical procedures where fat grafts may be included, including facelifts, abdominoplasty, liposuction, the treatment of open wounds, and others that I've mentioned earlier.

In reviewing the draft guidance documents, I'd like to highlight some key concerns. With respect to the adipose draft guidance, we would like the FDA to expand the categorization of adipose tissue from exclusively structural to both structural and nonstructural, depending on its intended use. In addition, we would like the FDA to revise their position that decellurizing the adipose tissue necessarily diminishes its ability to perform its structural function.

With respect to the same surgical draft guidance document, we would appreciate it if the FDA would clarify that centrifugation of liposuction aspirates in preparation for autologous fat grafting falls within the same surgical exception.

The next few slides highlight specific language changes that the American College of Surgeons believe will address these concerns. Our understanding is that the FDA has requested specific changes to the draft and that's why we're providing them here.

With regards to adipose, we request that the FDA revise the guidance to recognize adipose can have both structural and nonstructural functions. We also request that the FDA examine the individual HCTP and the manufacturer's objective intent to determine whether it is structural or nonstructural rather than focusing on the tissue character category, for example adipose tissue.

In addition, we believe that

decellularization and delipidation in and of itself should not be more than minimal manipulation. FDA guidance noted that adipose can have connective properties similar to dermis. As such, decellularization of adipose similar to dermis should not result in more than minimal manipulation. Examples noted below.

With regards to the same surgical guidance document, we believe that a new FAQ should be added in the guidance to clarify which -- what certain manufacturing steps beyond rinsing, cleansing or sizing are generally included within the exception, including centrifugation of liposuction aspirates in preparation for autologous fat grafting.

Before I actually say thank you, given some of the comments I heard this morning with regards to registries, I wanted to make one comment with regard to that. You'll be hearing some comments later today and tomorrow from the American Society of Plastic Surgeons and the Plastic Surgery Foundation regarding the graft

registry, which is a registry which was initiated this year and is now currently up and running among member surgeons. That is currently gaining a significant amount of impetus and data within it as mentioned. As would be desired, it's a real-time registry with real-time data giving real-time analysis of that data. So I would appreciate if the FDA would consider that registry in its deliberations.

Again, many thanks for providing me the opportunity to speak today. I hope that I have been able to educate you slightly on fat grafting across various surgical specialties, as well as provide some key recommendations to ensure that our patients have continued access to these key procedures. The American College of Surgeons is committed to ensuring patient safety while still providing the most innovative surgical techniques for our patients. And I'll welcome any questions that you have later on. Thank you very much.

DR. WITTEN: Thank you. Our next speaker is from the American Society of Plastic

Surgeons.

DR. RUBIN: Good afternoon. First I'd like to thank the FDA for hosting this Part 15 hearing. My name is Dr. Peter Rubin, and I'm here on behalf of the American Society of Plastic Surgeons to further discuss issues relevant to board certified plastic and reconstructive surgeons and our patients.

Before I begin, I would like to provide a little more background on the ASPS and our work. As this slide indicates, the Society represents nearly all board certified plastic surgeons practicing in the United States.

One key issue raised by the draft guidances is the appropriate regulation of autologous fat grafting. Therefore, the focus of my presentation will be to provide more background on such procedures, including its long history, as well as provide specific recommendations to the draft guidances to address any concerns board-certified plastic surgeons may have with respect to fat grafting. As this slide indicates,

fat grafting is a form of tissue grafting in which fat is acquired from the patient using a simple hollow bore cannula placed into the subcutaneous tissues to which suction, vacuum suction, is applied. The tissue is then gently centrifuged to separate the layers, a very minimal processing step, before being reinjected into the same patient.

Given the simplicity of the procedure it should not be surprising to note that fat grafting has actually been around for over 100 years, from Gustav Neuber first transplanting fat in 1893 to recognition of the regenerative potential and the development of injectable methods. And the ultimate expansion of application to numerous reconstructive applications throughout the body, including military applications.

As this slide demonstrates, fat grafting is really integral to the practice of plastic surgery for a variety of clinical purposes and not surprisingly has been widely integrated into routine plastic surgery practice with many

thousands of cases being done across the nation every year, and especially as it relates to breast cancer reconstruction. Seventy percent of U.S. plastic surgeons have used fat grafting techniques for breast operations, and

percent of those plastic surgeons said that they use fat grafting for reconstruction techniques and often apply fat grafting along with implants or flap procedures. Fat grafting is a key option for treating other post mastectomy conditions, including reversing damage caused by therapeutic radiation, the remodeling effects, and reducing breast implant-related breast pain and post-mastectomy pain.

I'd like to take a minute or so to explain the relevance to breast reconstruction. As we all know, breast reconstruction aids in restoring the whole person after a woman has undergone surgery to remove breast cancer. Several federal laws have helped preserve and protect a woman's ability to have breast reconstruction surgery and critical to many of

those surgeries is the ability to use fat grafting. With that in mind, you can imagine our concern with this particular example within the draft adipose guidance suggesting that fat grafting to the breast, such a widely practiced procedure with great benefits to our patients, is considered non-homologous use. As we see in the guidance document, in Example B3, this states that adipose tissue is recovered and processed for injection to the breast as reflected by the labeling, advertising, or other indications of the manufacturer's objective intent for non-implant based augmentation.

The breast is composed of lobes of glandular tissue and branching ducts interspersed with fat and ligaments that support the breast and give it shape and nerves, blood vessels, and lymphatic tissues. The basic function of the breast tissue is to produce milk, lactation, after childbirth. Because this is not a basic function of adipose tissue, using HCTPs from adipose tissues for breast augmentation would generally be

considered a non-homologous use.

Now this language is actually very problematic and has unintended consequences. As this slide highlights, fat grafting to the breast is most certainly a homologous use. Adipose tissue, which is naturally present in breast tissue, is a structural component. As a structural component is injected to the breast to preserve the structure and function of the secondary sex organ, and as such should be considered homologous use. Moreover, lactation is not the sole function of the breast. Lactation is only a function of the breast during the very limited period following childbirth. In contrast, throughout a woman's adolescence and adulthood, the breast's main function is that of a secondary sex organ.

To further highlight this point, I'd like to show this illustration which clearly depicts the presence of fat tissue in the breast as a normal structural component throughout the breast. The basic function of adipose tissues

includes providing structural support to define the shape of the human body. Autologous adipose is used to supplement, repair, and replace the breast tissue during breast augmentation or reconstruction. Therefore, this is a homologous use of adipose.

I'd like to further emphasize that no method of breast reconstruction restores lactation. Implant-based reconstruction restores form but not lactation. Fat-based breast reconstruction has been around for decades and also does not restore lactation. A very significant unintended consequence of this draft guidance is that it will eliminate the gold standard for breast reconstruction surgery, the free flap procedure. As we see in this diagram, the free flap procedure is a process by which a mass of adipose tissue is removed completely and then reconnected by microsurgery. So completely removed and transferred to another part of the body or reimplanted by microsurgery. Without a change to the draft guidance document, the gold

standard procedure would not be allowed.

Given these concerns, we respectfully suggest a modification of the language to ensure that women have access to all options for breast reconstruction. The suggested language that we propose is that we suggest that you modify Example B3 so that it reads, "Adipose tissue is recovered and processed for injection into the breast as reflected by labeling, advertising, or other indications per the manufacturer's objective intent for nonimplant breast augmentation." Because adipose is already within the breast to provide structural support and shape, using HCTPs from adipose tissues for breast augmentation or reconstruction would generally be considered a homologous use.

The language should not distinguish between breast augmentation and breast reconstruction. And the basic language should acknowledge that the breast has multiple functions and not rely on the basic function.

Once again I express my thanks to the

FDA for the opportunity to present on behalf of the American Society of Plastic Surgeons and our patients. Thank you.

DR. WITTEN: Thank you. Our next speaker is from the Biologic Orthopedic Society.

DR. MISHRA: Good afternoon. I'd like to thank the FDA panel members for organizing this important meeting. I'd like to thank the NIH for hosting us here in beautiful Bethesda. And I'd like to introduce myself. My name is Dr. Allan Mishra, and I represent the Biologic Orthopedic Society.

I'm going to start today with why. Why am I here? I'm here because we need better treatments for our patients. The status quo is simply not any longer acceptable. And if we're going to change the status quo, we need to look for better solutions. And my suggestion for the panel, for the participants, and for the people who are watching online is that it's possible that the power to heal can come from within.

Now, the Biologic Orthopedic Society is

a group I started about four or five years ago and I thought there'd be 50 to 100 like-minded individuals. We are now over 5,800 professionals dedicated to advancing the research and development of biologic treatments for musculoskeletal disorders.

And what we've found and what I would -- almost all of us know this already intuitively, our bodies have amazing healing power. I'm going to give you three specific examples.

Who in here has cut themselves either shaving or a paper cut in the last week? Okay, so next time you do that, what happens? You bleed. And what do you do? Maybe you push on it, you put a little Band-Aid on it, and it gets better within a week.

As an orthopedic surgeon, most fractures, simple fractures, will heal with immobilization and a little bit of time. And what's interesting is your liver has the most robust proliferative capacity or generative capacity. If you could actually take out a lobe

of your liver, transplant it to somebody else, then that lobe of your liver will regenerate. So skin, bone, and liver are three specific examples of our body's ability to heal itself.

Now, other tissues need a little bit of a helping hand. Skin, bone, and liver don't always heal, but other tissues sometimes need more of a helping hand. And where can we get that? Well, what if the solution -- I mean, we're spending billions and billions of dollars on healthcare, but what if the solution to challenging healthcare problems actually existed within our own bodies? We've heard some amazing talks today already about how that's possible. And I'm going to suggest to you that it may be.

What are the areas that we can look at? The simplest three are blood, bone marrow, and adipose tissue. I'm very happy because we had to turn in our slides about six weeks ago. I had to pick one of these three to focus on, and for the next four or five minutes I'm going to focus on blood.

All right, what I have for you is four specific points I'd like to make. We heard a little bit about this before, but blood is safe. Millions and millions of transfusions have gone on for decades in blood and blood products successfully. Literally blood saves lives, okay? But components of blood are not drugs, okay. That's my second point. My third point is blood is connective tissue. And this will go to the homologous use part of the draft guidance documents. And my fourth point is my most important one, and we'll talk about this in detail. We need to move at the speed of war. We're here talking about stuff that is really technical and challenging to maybe get into the nitty-gritty, but our patients are out there waiting for us to come up with better solutions for them. This is really serious business.

All right, number one, blood is safe. This is an example of using a component of blood called platelet rich plasma. This is a study I conducted over five years, 230 patients,

double-blind prospective randomized trial using PRP for chronic tennis elbow. And what we found is there are no significant adverse effects. And that's actually kind of pretty obvious. If you're using a component of your own blood and injecting it back into your own arm, it should be okay.

Surprisingly, we actually found an interesting signal of efficacy in that study. At 24 weeks, there were significantly more patients who were successfully treated compared to the control. And what should be embarrassing to the Americans in this room is that this data along with other data has allowed this to be approved in Europe and in Japan, but not technically in the United States. So the data that we generated here is being used overseas. And this isn't just my opinion. Published in The American Journal of Sports Medicine, the leading sports medicine journal in the world, this June was a meta analysis of randomized clinical trials concluding that PRP is of great clinical significance.

So if you think about it, blood is safe,

a component of blood can be used effectively, and blood is not a drug. A drug is a chemical or plant-derived substance that can be intended for a physiologic system. Blood is really a naturally derived product.

And I think this is my most important slide. Patients should be allowed to use components of their own body to help heal themselves. Let me maybe waste my time a little bit and say patients should be allowed to use components of their own bodies to help heal themselves. I think that's one of the most important things we can think about moving forward.

In the last two to three minutes I'll talk about how blood is connective tissue and how it should be used for homologous use. Connective tissue is supporting tissue that surrounds other structures. Blood, according to Pub Med Health, is included in that connective tissue list. So connective tissue is derived from embryonic mesoderm like other connective tissues and

consists of a matrix of cells designed to support other tissues.

So if you take those two and you put them together and you say, is blood connective tissue? And if you're going to use it to treat other types of connective tissue, it should be considered homologous use. And I can go into much more detail in comments that I'll submit.

The final thing that I'd like to talk about for two minutes, is we need to move at the speed of war. And I have to -- I can't take credit for this, this comes from a new friend of mine. He is Captain Tom Chaby. He is a former commanding officer of U.S. Navy SEAL Team 5, and he now is running the Warrior to Warrior Foundation, which is trying to help our veterans as they return from war with musculoskeletal issues and other significant problems. He really believes in two things: fast action and rapid reaction. And it's not just our vets that are facing incredible musculoskeletal problems, it's all of us. Almost everybody in this room probably

has something wrong with them from their musculoskeletal standpoint. So over 125 million Americans, $200 billion annually, 16 percent of all of our healthcare costs. And what's happening is an explosion of utilization. You're not going to die from the arthritis, probably not going to die from a disc herniation, but we're going to go bankrupt. Because if you look at the number of total needs that are expected in the next 15 to 20 years, it's going to skyrocket.

My question is, can biologics or components of our own blood or bone marrow help that? The answer is I think so. I think there's a really good chance that biologic orthopedics can provide transformative solutions.

So this is actually my MRI and my spine surgeon is actually sitting in the audience here today. But I underwent a discectomy about eight years ago, highly successful operation. But I would not like to go under the knife again. And is it possible for treatments like what we're talking about actually potentially avoid that?

The answer is yes.

And what do we need? In my last 30 seconds, we need regulatory systems that can adapt to the rapidly advancing science to help take care of our patients. And there are a few things that are out there, and one of them is the Regrow Act. It may not be perfect, but it allows for expedited, you know, approval and review processes that can sort of stimulate innovation and enhance patient care.

So again, I'd like to thank the FDA, I really appreciate the opportunity to speak. I'd like to thank the audience and the other speakers. And remind you, my little tag line, the power to heal comes from within. Thank you.

(Applause)

DR. WITTEN: Thank you. Our next speaker is from the Bipartisan Policy Center.

MS. MARCHIBRODA: Good afternoon. My name is Janet Marchibroda, and I'm pleased to provide comments to the FDA on behalf of the Bipartisan Policy Center. The Bipartisan Policy

Center, or BPC, is a nonprofit organization formed by former Senate majority leaders Howard Baker, Tom Daschle, Bob Dole, and George Mitchell. And what we do is we bring people together to negotiate and find common ground on issues such as economic policy, energy policy, immigration, and of course healthcare. Lots of easy things to focus on.

We commend the Food and Drug Administration for holding this public hearing to gain broad input on HCT -- on human cells, tissues, and cellular and tissue-based products and for your efforts to increase regulatory clarity. Thank you.

BPC's advancing medical innovation effort, led by former Senate Majority Leader Bill Frist and former Representative Bart Gordon, we made about 19 recommendations over the last year to reduce the time and cost associated with the discovery, development, and delivery of safe and effective medical products here in the United States. And we focused on a range of things

improving the medical product development process, increasing regulatory clarity, as we're talking about today, strengthening the ability for FDA to meet its mission, and other issues.

So getting to the point, one set of our recommendations that we released last year focused on the need to both clarify and modernize the regulatory framework for the use of human cells, in many cases, one's own cells, which we've heard about today, to restore healthy function in the human body.

The science of cell therapy has evolved considerably, as you well know, since 2001, when Part 1271 rules were first introduced. Today, we believe and many believe that cell therapies represent the next generation of groundbreaking treatments. It's amazing what we're seeing in the field of cardiology, neurology, oncology, and ophthalmology. And if you look at clinicaltrials.gov and you do a sort, I guess we've got like almost 5,400 clinical trials in this area, over half of which are focused on

cancer, which is a big priority for our country right now having just gotten the Moon Shot Recommendations that came out. And then interestingly enough, more than 100 trials are focused on each of the following areas. Things like heart disease, diabetes, kidney disease, burns and wounds, which we've heard about. So it's all very exciting. Not to mention the handful of trials that are looking at issues or diseases for which there is no cure, like Alzheimer's Disease and Parkinson's Disease.

So what we did is we convened a panel of nationally recognized scientists and experts over the last year to inform our recommendations. And many of them are with us or testifying over these two days. And our goals were really twofold. To enable patients to gain access in our country, not flying overseas, to safe and effective therapies. And then number two, to protect patients from unsafe therapies.

And as context for our comments on the four guidances, I want to just make a couple more

points. And this is important. I think it's driving the activity that's happening in the field today. Basically, there are only two pathways for moving forward, as you well know. We've got Section 361, the narrowly defined set of treatments that we're talking about over these two days. And those can be offered to patients with no premarket review, as you well know, by clinics that follow certain requirements. Okay, but then way over here there's all other therapies, which is the majority, require a full BLA and take up to a billion dollars and 10 to 12 years before they can be made available to patients. Even if a patient's own cells are used in many cases.

So our recommendations, our expert panel recommendations, focused on this need for a middle ground pathway or a tool that the FDA could use at its discretion to provide more flexibility between nothing and 10 to 12 years and a billion dollars. That's important context. I'm looking at my time.

This spring we updated our recommendations in the spirit of finding common

ground, which we do at the Bipartisan Policy Center. We listened to a handful of industry organizations and patient groups who felt more comfortable with not moving forward on a conditional approval, but actually leveraging your existing expedited programs, which a majority, more than 60 percent, of drugs are actually approved today under those expedited programs. So we're hoping that will move forward.

I think the lack -- I'm watching my time -- the lack of the middle ground pathway has created -- you know, we've all looked, the more than 500 clinics, you know, that are out there, some of which may -- we don't know, there was just a Google search that was performed -- may be operating outside of the practice of medicine. So you have that on the one hand, and then you have like -- you can count on less than two hands, maybe less than one hand, the number of cell therapies that have been approved under traditional processes.

I'd like to in my two minutes turn now

to the guidances upon which you seek input today. We've got detailed written comments on all four of the guidances as written. There's just one major thing we want to raise. As written, the guidances limit the use of adipose stem cells to the underlying characteristics of the tissue in which these cells are located. For example, the structural support or padding and cushioning against shock and fat issue. I know a number of folks have raised this today. We believe the current language in the guidance is inconsistent with the language and intent of the definition of minimal manipulation in 1271. And you've heard this from many folks who have spoken today. We believe that patients should have the right to use their own cells for orthopedic and other appropriate uses now if registered and licensed clinics observe the protections included in 1271 without having to go through this mountainous regulatory process.

As an aside, I also want to say for the record we really like this idea of a registry that

a lot of folks have been talking about today.

Again, we plan to submit more detailed written comments by your deadline. Thank you again. Thank you very much for holding this public hearing and for listening and giving all of us the opportunity to provide constructive feedback. This is a timely and important issue for patients in the United States. Things have changed. The science has evolved. And a flexible regulatory approach that preserves the gold standard, preserves the gold standard for safety and efficacy and also takes into account the unique aspects of cell therapies is needed to support patient access to treatments that show great promise for treating diseases today. Thank you.

DR. WITTEN: Thank you. Our next speaker is from the California Institute of Regenerative Medicine.

DR. MILLS: Greetings, and thank you, members of the Food and Drug Administration for holding this very important meeting. My name is

C. Randal Mills, and it is my great honor to be here today representing the California Institute of Regenerative Medicine, or CIRM. CIRM is the largest and most comprehensive organization dedicated for the advancement of stem cell and cell therapies anywhere in the world. It's a $3 billion organization. We have 12 major research facilities throughout the State of California, 3 state-of-the-art stem cell alpha clinics, a genomic center, a 3,000 cell line IPS bank, and over 300 projects in development from discovery all the way through phase 3 clinical trials.

Our mission at CIRM is to accelerate stem cell treatments to patients with unmet medical needs. And so that's why we're here today. As we see it, there are two problems that exist right now. And at least the first we can agree on. The first is the proliferation of stem cell clinics offering treatments for which there is little or no data to support safety and efficacy of the therapy. The second problem is the lack of progress being made through the

conventional biological license application pathway that exists for stem cells.

So basically, what we're seeing is a lot of what we don't want and not nearly enough of what it is we do want. And we have to ask ourselves why are we seeing this? And we think there are two factors that are driving the current situation.

The first -- and this can't be understated -- is that patients are really suffering. There is very real demand and very real need that is not being met in the patient community by conventional medicine.

The second is that the current regulatory paradigm that exists is binary. It exists in either an on or an off pathway. Drugs can either -- specifically stem cell therapies -- can either come to market legally under what we'll call the exemption pathway or the off pathway. It takes days. There's absolutely no pre-market requirements. It costs almost no money. If you don't fit into that exemption, then you go through

the on pathway. And the on pathway couldn't be further from the off pathway. It takes decades. It costs billions of dollars. If you're a stem cell, nothing's gotten through it. And so it's this very binary pathway.

So the results that we're seeing today, the proliferation of things going through the off pathway, isn't a surprise. It's completely predictable. And it's driven by two things. One, a very real demand, and two, a pathway that gates between these two things.

And I want to sort of take an opportunity to create an analogy. Imagine it's 1903 and we're standing on the beach in Kitty Hawk, North Carolina, and the Wright Flyer, the first airplane, has just flown. And the FAA comes along and says, hi, you don't know us, but we're the FAA and we're here to help. And anyone that's been in biologics knows that joke. And we're here to help and here's the deal. If it looks like the Wright Flyer and it resembles the Wright Flyer -- and we'll give you four different tests that you

can use -- then we'll let you develop more of these airplanes as much as you want without any regulation whatsoever. But if it's anything other than the Wright Flyer, we're going to regulate you like we're going to regulate the 787 Dreamliner.

That's basically what we have today. If you're not willing to make a generational change in a paradigm of how you're developing a cell therapy, if you want to use it in -- if you want to use cells to do something a little bit outside of what the FDA considers homologous, it doesn't step up a little bit, it steps up generationally. And that's a real problem. There's a practicality aspect to that. A physician can't meaningfully comply with biological license application regulations. They won't do it. It's an impossibility for a physician working in their own practice to take a cell therapy and run it through the BLA pathway.

And so what we're here today -- I'll just get to sort of the point -- is to advocate for something in between. We don't like and are

not happy with the proliferation of these stem cell clinics. But we also recognize that the answer to that isn't simply by plugging the loophole, basically. And the reason for that is the demand that exists is very real.

If you imagine water running down a hill, what we're trying to do here today with these guidance documents is constrict the pathway that that water is flowing down the hill. But the water is flowing down that hill because the demand or the gravity at the other side of the equation is real. And so by blocking that demand, that water will find a way around it. So what we're asking for, we're hoping FDA will seriously consider, is some alternate pathway. Don't just constrict the water running down the hill, tell the water where it is you want it to run. Create an alternative regulatory pathway that physicians and clinics and people can comply with that's practical and doable and not the on or off binary system that currently exists today. We think this is what FDA actually intended to do when they

first started discussing the current regulatory paradigm almost 20 years ago. And we think it's good and appropriate.

So with that I will stop talking. And thank you again very, very much for holding this hearing and for taking these considerations seriously. We do appreciate it.

(Applause)

DR. WITTEN: Thank you. Is there someone from California Life Sciences Association?

DR. RAVITZ: No, I'm actually with the Coalition of Wound Care Manufacturers.

DR. WITTEN: Okay. So next we'll hear from --

DR. RAVITZ: Nothing like being the last speaker of the day, right?

DR. WITTEN: We'll hear from the Coalition of Wound Care Manufacturers.

DR. RAVITZ: Okay. My name is Karen Ravitz. Good afternoon. And I am the healthcare policy advisor for the Coalition of Wound Care Manufacturers. The Coalition represents leading

manufacturers of wound care products used by patients for the treatment of wounds. Our members manufacture products that are included in these guidance documents. Thus, the Coalition has spent considerable time working with our members in order to present our many concerns and recommendations, with the majority of them being provided in our formal written comments.

We thank the FDA for holding this enlightening public meeting and for allowing me to present our testimony. We agree with many of the recommendations and comments that were provided to the FDA today regarding minimal manipulation and homologous use, including, but certainly not limited to, the following.

The elimination of the term "main function" from the minimal manipulation guidance document and instead the agency should continue to utilize the term "basic function or functions," which is already required in the regulations.

We request that the FDA clarify these documents in order to help manufacturers clearly

understand the regulatory pathway. We agree that examples previously provided should be put back into the guidance documents. And additional examples, including at what point a tissue structure must be preserved to be considered minimally manipulated, should be placed into these documents to provide additional clarity.

We believe that the recommendation that was stated today regarding providing flowcharts to demonstrate the evaluation of products would also be helpful.

We also agree that the change regarding how minimal manipulation is determined and specifically the focus on the main function of the tissue in the donor rather than by the function of the tissue in the recipient is problematic. The analysis should be based on the effects that the processing has in the tissue's utility for reconstruction, repair, or replacement in the recipient.

We also heard that the FDA had stated in the past that amnion may be used for wound healing

when cytokines are present, meaning that it's not decellularized. We agree with this statement and urge the FDA to continue to permit amnion in their homologous use considerations.

Several presenters stated that extracellular matrix signals evoke recipient cell responses, which suggests that structural tissues have basic functions beyond physical support and/or protection. We agree with this argument.

And finally, we agree with the following two recommendations: that the FDA expressly acknowledge that some tissues have both structural and nonstructural functionality, and that the FDA provide scientific explanations of different applications of minimal manipulation. These recommendations highlight our most important issue, which is the process that the FDA has used in issuing these guidance documents, especially the guidance on minimal manipulation.

We believe that these types of documents serve as guidance to interested parties. The purpose of a guidance document is to allow the

industry to know what the FDA's current thinking is on a topic. There are regulations that are issued with respect to the specific topics of these draft guidance documents that should not be in conflict with the guidance itself. The guidances should provide clarity to the regulations. They should not be adding new requirements to the regulations, which we believe is what these guidance documents do.

Too often the FDA issues guidance documents that makes substantive policy changes without going through the appropriate notice and comment period. A concern not only to those in the industry, but also to members of the Senate Committee on Health, Labor and Education, or Education and Labor. These documents fit into this category. For instance, given the expanded definition of "minimal manipulation" to reply upon the main function in order to determine whether a tissue type is considered structural or nonstructural imposes new limitations under the current regulation and are considered substantive

changes. As such, this draft guidance should have been issued in accordance with a notice and comment proceedings required by the Administrative Procedures Act, or the APA.

Section 553 of the APA requires the publication of proposed agency rules be followed by a period of time for consideration and comment by the public. A notice and comment period is not required if an agency issues an interpretative rule or a general statement.

These guidance documents are not an interpretive rule, nor are they a general statement. Rather, they contain material changes to existing regulation with additional requirements being imposed. Case in point with the examples provided all day today regarding the new term "main function" and the material change in how minimal manipulation is determined and specifically the focus on the main function of the tissue and the donor rather than the recipient.

The Coalition recommends that the FDA work with interested stakeholders. This meeting

was a first good step, and as a result, throughout the day the FDA has been provided with many great recommendations regarding these documents, which we hope you adopt.

We also recommend that the FDA take one of two steps moving forward. Either the FDA should eliminate the substantive policy changes from these guidance documents and continue to work with stakeholders to provide additional examples and clarity to the HCTP guidance documents or, if the FDA wants to make substantive changes, they should withdraw these guidance documents and instead go through the appropriate regulatory process.

Whether the FDA maintains the current guidance documents with added clarifications provided or whether substantive changes are proposed within the appropriate regulatory process, we hope that the FDA seriously considers the recommendations made here today by the many organizations that provided testimony. Thank you for your time.

DR. WITTEN: Thank you. I'll now ask the panel if they have questions for the speakers.

MS. ZAVAGNO: I have a question for Dr. Allan Mishra.

DR. WITTEN: Speak into the mike.

MS. ZAVAGNO: I'm wondering if you can explain to me why you think blood is not a drug? That was a big part of your presentation.

DR. MISHRA: Yes. I think it's a paradigm shift. So if we think of drugs as manufactured products or chemical-derived products that we distill from plants or make them in big bioreactors, that's a drug. If I think of your blood, it's an incredibly complex system of hundreds of proteins that are natural to you. And to me that is not a drug. So that's where I'm parsing it in a different paradigm perhaps than the FDA. But I don't think of it -- I don't think of myself as being -- as drugs flowing through my body right now. I think of blood flowing through my body.

MS. ZAVAGNO: You are aware that blood

is a licensed product, right, by the FDA? I just wanted to point that out. And I also wanted to point out or ask you if you were familiar with the definition of an HCTP, which is --

DR. MISHRA: I am, and I --

MS. ZAVAGNO: -- blood and blood components.

DR. MISHRA: I again appreciate the opportunity to speak here. I utilized my eight minutes perhaps not in exactly the way that was described, but I utilized it because I feel very passionate about -- perhaps some of the other speakers were more eloquent than I was about a paradigm shift or a need for a middle pathway in terms of how we regulate biologic products, whether it's blood, bone marrow, or adipose tissue. The water analogy is a fantastic one. If any one of you or anyone in this room who's not a clinician followed us around, it is not a trickle, it is a waterfall of a problem, an avalanche of snow coming down the mountain that we are not adequately prepared for.

And frankly, as Americans, we're not really treating it like an emergency. And I didn't realize that until this summer when I met Captain Chaby, and I realized our veterans are coming back and they're seeking out some of these regenerative medicine products because they're dissatisfied, as we are, with what's available. And I don't think we can iteratively consider options. I think we need to consider this almost an emergency in terms of how we can perhaps light a fire under all of us to say we can't just talk about this for another 2 years, 5 years, or 10 years. And we don't have the money as clinicians to do a BLA.

And I was actually blocked by an IRB because we had to go to the FDA to get your blessing to do a study. And it was an enormous challenge to figure out if we could marshal the resources to determine whether we needed your approval or not.

So what you do is incredibly important and incredibly impactful for those of us at the

vanguard of trying to develop new products for our patients. Because what we have right now, it doesn't even always work as well as we want it to. And it's going to drive us into bankruptcy if we don't come up with better solutions for the problems that I'm facing every day in my clinic.

MS. ZAVAGNO: All right. Thank you.

DR. MISHRA: Thank you. (Applause)

DR. ANATOL: I have two questions for ARM. So I'll start with what I think is the easy question first. You referred to the guidances needing some clarity around product characterization. Can you give a little bit more detail? Like I'm not sure if you were referring to processing steps or something else.

DR. WERNER: Well, I think what we were talking -- that was in the context of that we represent folks who are trying to do research and develop products across the spectrum, right? And how FDA defines certain of these key terms will determine how they're classified. So perhaps classification is a better word than

characterization in this context. But that's what I was referring to.

DR. ANATOL: Okay. And then -- thank you. You also suggested that we provide more examples. I think both around minimal manipulation and homologous use. Do you have specific examples in mind?

DR. WERNER: In our written documents we do.

DR. ANATOL: Okay.

DR. WERNER: Yeah.

DR. ANATOL: Thanks.

DR. WERNER: And we have the sample flow -- people talked about -- we talked about flowcharts. We have samples of those, too.

DR. ANATOL: Okay. Great. Thanks.

DR. WERNER: Mm-hmm.

DR. WITTEN: I have a question for the speaker from AABB. In your talk you requested a number of things, I think, related to the guidance documents. Thank you for commenting on the guidances. And one was more examples of

nonstructural versus structural tissues. And you provided a couple of examples of tissues. But it wasn't clear what -- do you have a viewpoint on that, or do you have recommendations or some examples that you'd like to suggest we consider as examples to provide clarity about structural and nonstructural tissue?

DR. KAMANI: Well, there are two points we are trying to make. One is that the list needs to be more comprehensive so that at least those tissues that are tissues and cells that are being collected currently either for the purpose of storage or manipulation are at least included in those lists. And secondly, it's not clear because the guidance is silent on a couple of those tissues whether it would belong to one category or the other. And the example we chose was cord tissue, which currently is being stored by a number of facilities for the purpose of future use as a source of mesenchymal stromal cells. And the other is tissue such as the thymus gland or thymic tissue, which occasionally is used for

transplantation.

DR. WITTEN: Okay, thanks, that's helpful. Other questions from panel members?

MR. WEINER: I had one question, if I could. I think it was the Alliance for the Advancement of Cellular Therapies. I just wanted to clarify something on your -- as I understood your talk, it sounded like you were giving a detailed proposal for how registries might be used to augment phase 2 data.

DR. MILLER: Yes.

MR. WEINER: And probably with regard to lack of sufficiently powered data. And walking through it all, I was just curious how you'd consider your proposal to compare to sort of a more typical through a phase 4 approach to getting additional data for post market.

DR. MILLER: I think there is an analogy at a post marketing surveillance. I mean, that's really what you're saying. There's a product that's out there. We believe it's able to be used and commercialized, and yet you want a much more

in-depth look at the safety and efficacy that's proven in subsequent analysis. And I think this is getting out of the clinical trial and the rigor of that where sometimes you're excluding a lot of patients that would be not qualifying by that protocol criteria that would really enhance the knowledge of the overall applicability of a specific cell therapy or strategy to a wider number of patients.

MR. WEINER: Thank you.

DR. MILLER: Yep.

DR. WITTEN: Okay, before we close, I have two announcements to make. One is, for those of you who are returning tomorrow -- and I hope that and encourage people to do so -- please bring your badge again, it will simplify things. So bring your badge back. And the second is that some woman's jewelry was found in the women's bathroom. If you have lost an item, you can retrieve it from the NIH library. So that's just for anybody who's lost something.

So now, just to close, I'd like to thank

everyone, the speakers for their presentations and the audience, whether in person or by webcast, for your attention in today's meeting on behalf of the FDA panel. We had a very full day of interesting and insightful comments. Along with the comments of the dockets, we'll consider these as we finalize the guidances.

The hearing is concluded for today and will reconvene tomorrow at 9:00 a.m. Thank you for your participation.

(Whereupon, at 4:21 p.m., the PROCEEDINGS were adjourned.)

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CERTIFICATE OF NOTARY PUBLIC

DISTRICT OF COLUMBIA

I, Carleton J. Anderson, III, notary public in and for the District of Columbia, do hereby certify that the forgoing PROCEEDING was duly recorded and thereafter reduced to print under my direction; that the witnesses were sworn to tell the truth under penalty of perjury; that said transcript is a true record of the testimony given by witnesses; that I am neither counsel for, related to, nor employed by any of the parties to the action in which this proceeding was called; and, furthermore, that I am not a relative or employee of any attorney or counsel employed by the parties hereto, nor financially or otherwise interested in the outcome of this action.

(Signature and Seal on File)

Notary Public, in and for the District of Columbia

My Commission Expires: March 31, 2017